

Award Number: W81XWH-12-2-0129

TITLE: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

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Durham NC 27705-4677

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Fort Detrick, Maryland 21702-5012

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13. SUPPLEMENTARY NOTES				
14. ABSTRACT <p>The purpose of this research is to determine if FDA approved Valproic Acid, commonly used for migraine headache prophylaxis, will also be effective in the prevention of chronic neuropathic pain. Additionally, this research will define the alterations in DNA methylation and gene expression that occur after injury and the extent that valproic acid, a known modulator of DNA methylation, will prevent the epigenetic effects that lead to the development of chronic post-surgical pain.</p> <p>Because this is a double-blinded, randomized controlled trial, we do not anticipate any major findings until the study is closed and the blinding removed. We are pleased to report that there have been no SAEs attributed to study drug, and that the study drug appears to be well tolerated in a generally older, debilitated population.</p> <p>With enrollment less than anticipated, Dr. Buchheit discussed the addition of Duke as an enrollment site with Patricia Henry PhD, Science Officer. On 02Oct14 we received notice of approval for the revised Scope of Work and re-budget request from Lisa Wells Roark, DOD Contract Specialist.</p>				
15. SUBJECT TERMS Amputation, Postamputation pain, Post-surgical pain, Neuralgia, Epigenetics, Valproic Acid, DNA Methylation, Neuropathic pain				
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INTRODUCTION

Chronic pain is a significant problem in patients undergoing surgery following military trauma and chronic vascular disease. Symptoms are typically treated with medications such as narcotics, anti-inflammatory drugs, and local anesthetics. Despite these therapies, more than 50% of patients who have an amputation or significant limb injury experience long-term chronic pain. Chronic pain in military personnel and veterans may impair their ability to ambulate or wear a prosthetic device, and may ultimately require the use of chronic narcotic medications. Although sometimes effective for pain, chronic narcotic medications also carry risks of sedation, confusion, and possible addiction. Identifying preventive mechanisms that can be employed at the time of surgery is of utmost importance for military and veteran health systems. Valproates such as valproic acid have a unique advantage over other classes of medicines used for neuropathic pain, as this drug actually modifies the epigenetic mechanisms, such as DNA methylation, and therefore may demonstrate efficacy in preventing the transition from acute to chronic pain. In this study, we will additionally define the gene expression changes that occur in the transition from acute to chronic pain, and any effect that valproic acid may have on these genes.

In summary, this research will investigate the effectiveness of valproic acid vs placebo when added to regional anesthesia in the prevention chronic pain after amputation, stump revision, or surgery for mangled limb with neurologic damage. It will also define the gene expression changes that occur after surgery and the ability of valproic acid to prevent the epigenetic changes that lead to the development of chronic pain.

KEYWORDS

Amputation, Post-amputation pain, Post-surgical pain, Neuralgia, Epigenetics, Valproic Acid, DNA Methylation, Neuropathic pain

OVERALL PROJECT SUMMARY

We received all approvals necessary to begin enrollment at the Durham VAMC on 22Nov13. During Year 2 of this study (1st year of enrollment), we experienced lower than anticipated numbers of eligible subjects. To address this issue, we requested that Duke University Medical Center be added as an additional enrollment site and received approval from DOD on 02 Oct14 and HRPO on 30Jul14. We received Duke IRB approval for enrollment at DUMC on 19May14.

Below is a detailed list of events and accomplishments during Year 2 of this project.

Durham VAMC

2013

OCTOBER	In-services and meetings with VAMC nursing and all study personnel while awaiting CRADA approval from VAMC
NOVEMBER	Duke/VA CRADA approved; start of enrollment at Durham VAMC.
DECEMBER	Two patients enrolled in Quarter 1.

2014

FEBRUARY	Preliminary discussions with DOD, Col. Buckenmaier and Duke regarding addition of Duke as a study site to improve enrollment
MARCH	Three patients enrolled in Quarter 2
APRIL	Protocol amendment submitted to Duke IRB for Duke patient enrollment
MAY	Numerous meetings at Duke (Investigational Drug Service, Limb Loss Clinical Nurse Specialist, in-patient team) to discuss logistics and screening process

- JUNE Four patients enrolled during Quarter 3.
- First 2 patients enrolled at VAMC complete the study, finishing their 6-month visits.
- JULY Received HRPO approval for Duke as an enrollment site (Attachment 1)
- SEPTEMBER Request for Human Studies Continuing Review was submitted to DVAMC IRB for the 09Oct14 IRB meeting date (Attachment 2). The IRB requested that the previously approved Informed Consent Form be reformatted into the DVAMC IRB June 2014 format (Attachment 3). The reformatted ICF, without changes, was submitted with this Continuing Review request.

Duke University Medical Center

2014

- MAY Received Duke IRB approval for patient enrollment at Duke University Medical Center
- JUNE Submission of requested Duke protocol documents, IRB approvals and re-budget information to Lori Walther/HRPO, Dr. Patricia Henry, Science Officer and Lisa Wells Roark, Contract Specialist requesting the addition of Duke University Medical Center as a study site for enrollment.
- JULY HRPO approval for enrollment at Duke University Medical Center The protocol is approved for adult subjects (18 years and older) undergoing surgery for amputation, stump revision, or surgery for limb injury with neurologic damage. The total number of subjects approved is 420 across all sites; 155 subjects are approved for enrollment at Duke University Medical Center.
- AUGUST In-service for the Duke Acute Pain Service and PI training on the study protocol
- Coordination with Duke Pharmacy
 - The study at Duke was approved for Continuing Review by Duke IRB and given an expiration date of 28Aug15.
 - Dionne Apedjihoun, CRC met with Nancy Payne, Duke Clinical Nurse/Limb Loss Specialist to trouble shoot potential patient recruitment for in and out-patients and to delineate a mechanism for screening and potential enrollment.
- SEPTEMBER Dr. Hsia, Co-I, and Dionne Apedjihoun met with Donna Hamel, Clinical Trials Project Leader at Duke Clinical Research Unit to discuss storage of biological samples prior to shipping to GSRB. Samples will be stored at two Duke locations: the -20°F at Hanes House and -80°F at Duke South.
- Continuing Review Submission Form, required and supporting documents were submitted to HRPO for the study at Duke.
- OCTOBER Received DOD approval for patient enrollment at Duke on 02Oct14 (Attachment 4)
- Meeting with Duke Investigational Team to finalize enrollment process and protocol 15Oct14
 - Enrollment of first study subject at Duke 15Oct14. Four patients have been enrolled at Duke/VA between 15Oct14 and 25Oct14.

Walter Reed National Military Medical Center

2013

- OCTOBER Duke research team visited WRNMMC research team in Bethesda to review the protocol, standard operating procedures and enrollment practices.

- DECEMBER Received WRNMMC IRB approval
- Submitted protocol to MRMC for secondary approval

2014

- MARCH Received MRMC secondary approval
- Mary McDuffie, Research Coordinator, visited Durham VAMC for training review
- APRIL Ms. McDuffie held an in-service for nursing staff
- First patient enrolled
- AUGUST IRB approval for protocol amendment to include patients having amputation surgery with a regional block.
- SEPTEMBER MRMC secondary approval received for protocol amendment.

- The first adjudication meeting is scheduled November 12, 2014.
- The chart below summarizes enrollment at Durham VAMC and Walter Reed. Duke is added as an additional enrollment site effective 02Oct2014.

Project Start Date 30Sep2012		
DVAMC <i>All approvals received 22Nov2013</i>	# Screened	#Enrolled
Year 2, Quarter 1	13	2
Year 2, Quarter 2	16	3
Year 2, Quarter 3	23	4
Year 2, Quarter 4	17	0
WRNMMC <i>All approvals received 11Mar2014</i>		
Year 2, Quarter 2	3	0
Year 2, Quarter 3	26	3
Year 2, Quarter 4	32	4
DUMC <i>Enrollment start date 15Oct14 (Yr3, Qtr1)</i>	To be reported in Yr3, Qtr1 Technical Report	
Total	130	16

With the request and approvals to add Duke University Medical Center as a study site (effective 02Oct14), we believe enrollment will improve substantially going forward. With this addition, a revised SOW was also approved and will apply starting in Year 3.

The SOW dated 23Aug13 is in effect for this year-end report and outlined below.

Task 1 (pre-study) – Human subjects approval (including HRPO)	Months 1-12	<u>Actual</u>
a. Duration (Durham VAMC), months 1-9		
b. Duration (WRNMMC), months 1-12		
c. Exempt from Review (Duke), months 9-10		
<u>Milestone</u> Pre-Study Task 1a – IRB & HRPO approval in Durham	Month 9	<i>Month 14</i>
<u>Milestone</u> Pre-Study Task 1b – IRB & HRPO approval at WRNMMC	Month 12	<i>Month 17</i>

Task 2 – Clinical Trial

Aim1: Determine the efficacy of regional anesthesia and valproate in reducing the incidence of chronic post-amputation pain.

Patients will be screened at the time of scheduling for surgery. We anticipate screening 19-20 patients per month to enroll approximately 6/month at each site. Subjects will receive either placebo or study drug (valproate) TID for 7 days.

a. Subject enrollment at DVAMC (210 pts)	Months 9-42	
b. Subject enrollment at WRNMMC (210 pts)	Months 12-42	
<u>Milestone</u> Task 2a – First patient enrolled in Durham	Months 9-10	<i>Month 14</i>
<u>Milestone</u> Task 2b – First patient enrolled at WRNMMC	Months 12-13	<i>Month 20</i>
c. First enrolled subjects seen at 3 month endpoint	Months 12-16	<i>Months 15-20</i>
<u>Milestone</u> Task 2c – Endpoint adjudication meetings at 6 & 12 months	Months 18-28	
d. Review of site enrollment targets		
<u>Milestone</u> Task 2d – Enrollment of 140 subjects	Months 24-26	<u>Projected</u> <i>Months 33-39</i>
e. Interim analysis	Month 30	<i>Month 40</i>
<u>Milestone</u> Task 2e – Endpoint adjudication meetings at 18 & 24 months	Months 30-40	<i>Months 40-46</i>

KEY RESEARCH ACCOMPLISHMENTS

Nothing to report.

CONCLUSION

Nothing to report.

PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

Nothing to report.

INVENTIONS, PATENTS AND LICENSES

Nothing to report.

REPORTABLE OUTCOMES

Nothing to report.

OTHER ACHIEVEMENTS

Nothing to report.

REFERENCES

NA

APPENDICES

Attachment 1 – HRPO Approval to add Duke as Enrollment Site, Revised SOW & Re-budget Detail

Attachment 2 – Durham VAMC Human Studies Continuing Review Submission

Attachment 3 – Durham VAMC reformatted Informed Consent Form

Attachment 4 – DOD Approval to add Duke as Enrollment Site

Attachment 5 – Valproate_Protocol_VAv28_Duke3_07242014

Attachment 6 – Duke IRB Approved Amendments (2)

Attachment 7 – Year Two Summary Quad Chart

From: Mahasreshthi, Parameshwar J CIV USARMY MEDCOM USAMRMC (US)

[<mailto:parameshwar.j.mahasreshthi.civ@mail.mil>]

Sent: Monday, March 10, 2014 8:38 AM

To: Buckenmaier, Chester C III COL USARMY USUHS (US)

Cc: Bennett, Jodi H CIV USARMY MEDCOM USAMRMC (US); Brosch, Laura R CIV USARMY MEDCOM USAMRMC (US); Thomas Buchheit, M.D.; Henry, Patricia A CTR USARMY MEDCOM CDMRP (US); 'mmcduffie@dvpmi.org'; Katopol, Kristen R CTR USARMY MEDCOM (US); Mary M Kirkley; Grants & Contracts E-Mail; Wells Roark, Lisa L CIV USARMY MEDCOM USAMRAA (US); Walther, Lori J CTR USARMY MEDCOM USAMRMC (US); 'Naoroz Islam'; 'krose@hjfi.org'; USARMY Ft Detrick MEDCOM USAMRMC Other CIRO; 'mary.kelleher.civ@health.mil'

Subject: A-18094 HRPO Initial Approval Memorandum (Proposal Log Number PT110575P1, Award Number W81XWH-12-2-0130) (UNCLASSIFIED)

Classification: UNCLASSIFIED

Caveats: NONE

SUBJECT: Initial Approval for the Protocol, "Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain," Submitted by COL Chester C. Buckenmaier, III, MC, Walter Reed National Military Medical Center, Bethesda, Maryland, Proposal Log Number PT110575P1, Award Number W81XWH-12-2-0130, HRPO Log Number A-18094

1. The subject protocol (version 2, 31 October 2013) was initially approved on 13 December 2013 by the Walter Reed National Military Medical Center (WRNMMC) Institutional Review Board (IRB). This protocol was reviewed by the US Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) and found to comply with applicable DOD, US Army, and USAMRMC human subjects protection requirements.
2. This greater than minimal risk study is approved for 210 subjects scheduled for amputation, stump revision, and surgery for limb injury with neurologic damage at the WRNMMC.
3. The Principal Investigator has a duty and responsibility to foster open and honest communication with research subjects. The USAMRMC strongly encourages the Principal Investigator to provide subjects with a copy of the research protocol, if requested, with proprietary and personal information redacted as needed.
4. Please note that a Research Monitor (RM) is required to be involved in DOD-supported research studies that are determined to pose more than minimal risk to subjects (DOD Instruction 3216.02, Nov 2011). If the duties of the RM could require disclosure of subjects' Protected Health Information outside a covered entity (i.e., the RM is not an agent of the covered entity), your institution may require the identity and location of the RM to be described in the study Health Information Portability and Accountability Act authorization.
5. The following are reporting requirements and responsibilities of the Principal Investigator to the HRPO. **Failure to comply could result in suspension of funding.**
 - a. Substantive modifications to the research protocol and any modifications that could potentially increase risk to subjects must be submitted to the HRPO for approval prior to implementation. The USAMRMC ORP HRPO defines a substantive modification as a change in Principal Investigator, change or addition of an institution, elimination or alteration of the consent process, change to the study population that has regulatory implications (e.g. adding children, adding active duty population, etc.), significant change in study design (i.e. would prompt additional scientific review), or a change that could potentially increase risks to subjects.
 - b. All unanticipated problems involving risk to subjects or others must be promptly reported by telephone (301-619-2165), by email (usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the US Army Medical Research and Materiel Command, ATTN: MCMR-RP, 810 Schreider Street, Fort Detrick, Maryland 21702-5000.

c. Suspensions, clinical holds (voluntary or involuntary), or terminations of this research by the WRNMMC IRB, the institution, the sponsor, or regulatory agencies will be promptly reported to the USAMRMC ORP HRPO.

d. Events or protocol reports received by the HRPO that do not meet reporting requirements identified within this memorandum will be included in the HRPO study file but will not be acknowledged.

e. A copy of the continuing review report and re-approval notification by the WRNMMC IRB must be submitted to the HRPO as soon as possible after receipt of approval. According to our records, it appears the next continuing review by the WRNMMC IRB is due no later than 12 December 2014. Please note that the HRPO conducts random audits at the time of continuing review and additional information and documentation may be requested at that time. At the time of continuing review, a summary of amendments must be submitted for inclusion into the study file.

f. The final study report submitted to the WRNMMC IRB, including a copy of any acknowledgement documentation and any supporting documents, must be submitted to the HRPO as soon as all documents become available.

g. The knowledge of any pending compliance inspection/visit by the Food and Drug Administration (FDA), Office for Human Research Protections, or other government agency concerning this clinical investigation or research; the issuance of inspection reports, FDA Form 483, warning letters, or actions taken by any regulatory agencies including legal or medical actions; and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.

6. **Please note:** The USAMRMC ORP HRPO conducts site visits as part of its responsibility for compliance oversight. Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research. Research records must be stored in a confidential manner so as to protect the confidentiality of subject information.

7. Do not construe this correspondence as approval for any contract funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds. It is recommended that you contact the appropriate contract specialist or contracting officer regarding the expenditure of funds for your project.

8. The HRPO point of contact for this study is Lori J. Walther RN MSN CCRP PMP, Human Subjects Protection Scientist II, at 301-619-2286/lori.j.walther.ctr@mail.mil.

PARAMESHWAR MAHASRESHTI, PhD
Human Subjects Protection Scientist
Human Research Protection Office
Office of Research Protections
US Army Medical Research and Materiel Command

Note: The official copy of this memo is housed with the protocol file at the Office of Research Protections, Human Research Protection Office, 810 Schreider Street, Fort Detrick, MD 21702-5000. Signed copies will be provided upon request.

Classification: UNCLASSIFIED
Caveats: NONE

Revised Statement of Work – August 5, 2014

CDMRP Log Numbers: PT110575 and PT110575P1

Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-amputation Pain

Background

Chronic pain is a significant problem in patients undergoing amputation following military trauma and chronic vascular disease. Regional anesthesia catheters provide control of acute post-amputation pain, but do not appear as effective in reducing the incidence of chronic pain. In a complementary manner, valproic acid has demonstrated efficacy in the treatment of chronic neuropathic pain, but its effect in the acute setting is unclear. Given valproate's unique ability to modify the epigenetic mechanisms involved in chronic pain (DNA methylation) we believe it will demonstrate efficacy in preventing the *transition* from acute to chronic pain. In this project we will determine whether the combination of perineural local anesthetic infusion and oral valproic acid reduces the incidence of chronic post-amputation pain. Additionally we will delineate the underlying metabolomic and epigenetic mechanisms involved in the transition to chronic pain and the epigenetic modifications induced by the use of valproate.

Project Sites and Research Staff

1. Duke University (W81XWH-12-2-0129)

*a. Durham Veterans Administration Medical Center (VAMC), Department of Anesthesiology
508 Fulton Street, Durham, NC 27705*

*b. Duke University Medical Center (DUMC)
2301 Erwin Road, Durham, NC 27710*

Thomas Buchheit MD	Principal Investigator	25%
Andrew Shaw MB BS	Co-Investigator	10%
Thomas Van de Ven	Investigator	37%
Hung-Lun Hsia	Investigator	36%
David MacLeod	Investigator	40%
Mary Kirkley	Project Manager	50%
Dionne Apedjihoun	Clinical Research Coordinator	100%
Magdi Elgasim	Clinical Research Coordinator	25%
Yi-Ju Li	Investigator, Statistical Geneticist	11.5%
Xue J Qin	Biostatistician III	23%
William White	Sr. Biostatistician, years 2-4 average	10%

2. Henry M Jackson Foundation for the Advancement of Military Medicine (W81XWH-12-2-0130)

a. Walter Reed National Military Medical Center/WRNMMC

8901 Rockville Pike, Bethesda, MD 20889

Col. Chester Buckenmaier	Partnering PI	2%
MAJ Laura McGhee, PhD	Scientific Director	5%
Kyung 'Nancy' Kwon	Research Manager	5%
Mary McDuffie	Research Nurse Coordinator	80%

Specific Aims

- **Specific Aim 1: Determine the efficacy of regional anesthesia and valproate in reducing the incidence of chronic post-amputation pain.**

Hypothesis 1: Valproate, a medication used for chronic neuropathic pain, may reduce the incidence of chronic pain if given at the time of surgery.

Summary of Aim 1: In a prospective, blinded randomized controlled clinical trial of 420 patients at **three** centers, we will determine whether the combination of perineural catheter infusion and oral valproate reduces the incidence of post-amputation pain when compared with local anesthetic infusion alone. “Control” patients will receive regional anesthesia catheters prior to surgery, and have catheter infusions of local anesthetic as per current standards of care. “Intervention arm” patients will receive valproate 250mg preoperatively, and then Q8 hours for 7 days post-operatively. The primary hypothesis is that patients treated with valproate will have an absolute reduction in the incidence of post-amputation pain at 3 months after surgery compared to the patients with placebo (in the control arm).

- **Specific Aim 2: Determine the role of differential DNA methylation in post-amputation pain syndromes and their treatment with valproate.**

Hypothesis 2: Analysis of epigenetic changes (DNA methylation) in patients with and without chronic pain will determine the changes that cause chronic pain.

Summary of Aim 2: Our approach to mechanistic discovery is outlined as follows. We use plasma metabolomics to indicate biochemical pathways that are over-represented in the disease state of interest, in this case valproate responders. We also require evidence of transcriptional differences for genes in these pathways in order to start to focus in on likely targets and/or specific candidates. We conduct these experiments using unbiased metabolomics (service provided by Metabolon) and analyze these data using MetaboAnalyst 2.0 - software provided by the University of Edmonton and designed specifically for identification of biochemical pathways of relevance in quantitative metabolomic datasets. Initially we conduct genome wide gene expression studies using Affymetrix arrays in our core facility. We analyze these data using Gene Pattern, software provided by the Broad Institute at Harvard, and specifically the GSEA algorithm. This conducts the same sort of over-representation analysis for the gene expression data. We then compare these lists and look for areas of co-overrepresentation. This approach provides 2 distinct lines of (unbiased) evidence that a certain pathway's genes are relevant. We next conduct a more reductionist approach using smaller (24 gene) plates custom designed for the pathway of interest using RT-PCR to confirm the array data and drill down on precisely which genes and transcription factors are most important. These upregulated transcription factors represent good therapeutic targets.

For epigenetic regulation we use exactly the same approach and conduct epigenome wide methylation experiments using the Illumina 450K Methylation Array in our epigenetic core facility. We confirm these data in our own lab using the Qiagen Epiect system on our RT PCR platform in analogous fashion to the expression data. Of particular interest in this project are the methylation differences between the intervention and control arms (i.e. did valproate change methylation within individuals and were these in mechanistically important genes?) and was there an interaction between clinical effect and baseline methylation status? The interaction of all these different, but related, lines of evidence greatly increases

the confidence we have in our data. By requiring consistency between metabolomic, expression and epigenetic datasets we greatly reduce the chance of false positivity.

Because so little is known about the biology of persistent amputation pain, we have adopted the above strategy in order to reduce the chance of a type 2 error - i.e. we miss a relevant positive result. By requiring the data themselves to drive the subsequent experiments we believe we maximize our chances of uncovering the true mechanisms. However, we do have certain hypotheses about why there is such a difference in the incidence and severity of post nerve injury pain and these were laid out in the original proposal. In brief we believe that persistent inflammation in both spinal cord and peripheral nerve leads to the development of allodynia and chronic pain. The fact that inflammation is essentially a process "delivered" to the disease site by the circulation (via invading leukocytes) means it is accessible by sampling peripheral blood. In this proposal we will not restrict ourselves solely to inflammatory genes, but we will certainly be paying very close attention to them.

We will analyze differential DNA methylation region (DMR) patterns of patients with different types of post-amputation pain, and determine the way they are altered by valproate sodium. We will prioritize pathways of interest using plasma metabolomics and confirm the functional relevance of these epigenetic modifications using circulating leukocyte gene expression signatures.

Project Tasks and Brief Descriptions

Timeline

1) Task 1 (pre-study) – Human subjects approval (including HRPO)

Months 1-24

- a. Duration (Durham VAMC), months 1-9
- b. Duration (WRNMMC), months 1-12
- c. Exempt Review (Duke), months 9-10 (for blood analysis only)
- d. Full Duke IRB Review to add Duke as 3rd enrollment site (August, 2014)

Milestone Pre-Study Task 1a – IRB and HRPO approval in Durham

Month 9

Milestone Pre-Study Task 1b – IRB approval at WRNMMC

Month 12

Milestone Pre-Study Task 1c – Duke IRB and HRPO approvals

Month 24

2) Task 2 – Clinical Trial

Months 9-46

Aim 1: Determine the efficacy of regional anesthesia and valproate in reducing the incidence of chronic post-amputation pain.

Patients will be screened at the time of scheduling for surgery. We anticipate screening 19-20 patients per month to enroll approximately 6/month at each site. Subjects will receive either placebo or study drug (valproate) TID for 7 days.

- a. Subject enrollment at DVAMC (55 pts)
- b. Subject enrollment at Duke (155 pts)
- c. Subject enrollment at WRNMMC (210 pts)

Months 9-42

Months 24-42

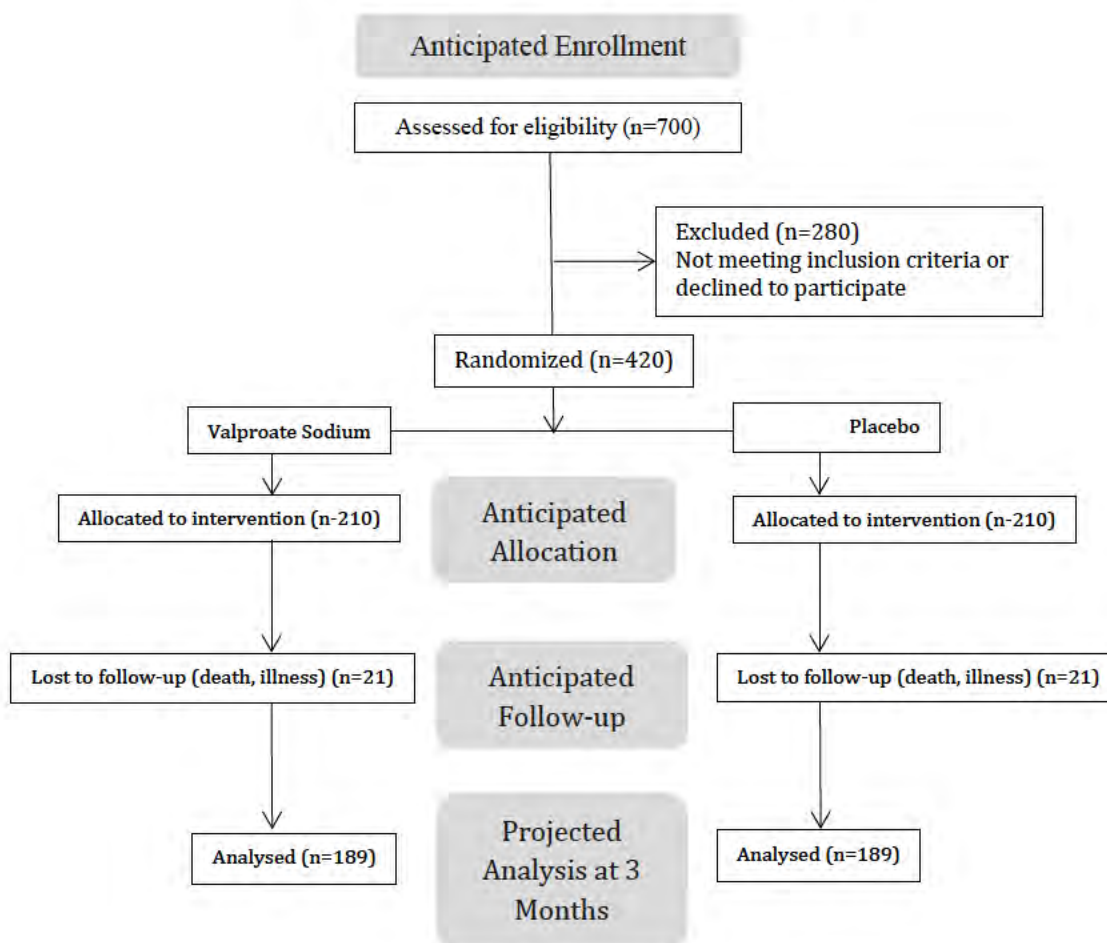
Months 12-42

Milestone Task 2a – First patient enrolled in Durham

Months 9-10

<u>Milestone</u> Task 2b – First patient enrolled at WRNMMC	Months 12-13
First enrolled subjects seen at 3 month endpoint	Months 12-16
<u>Milestone</u> Task 2c – First patient enrolled at Duke	Months 24
<u>Milestone</u> Task 2d – Endpoint adjudication meetings at 6 and 12 months	Months 18-28
d. Review of site enrollment targets	
<u>Milestone</u> Task 2e – Enrollment of 140 subjects	Months 30
e. Interim analysis	Month 30
<u>Milestone</u> Task 2f – Endpoint adjudication meetings at 18 and 24 months	Months 30-40
f. Projected enrollment of 376 subjects complete. Enrollment numbers will be monitored and we will likely request an EWOFF in Yr4, Qtr 4	Months 45-46
<u>Milestone</u> Task 2g – Endpoint adjudication meeting at 30 months	Month 45
g. Final subject follow-up after adjudication	Month 48
<u>Milestone</u> Task 2h – Close of clinical trial	Month 48

Valproate Sodium for Amputation Pain



Timeline

3) Task 3 – Metabolomic, Epigenetic and Gene Expression Analysis

Months 28-46

Aim 2: Determine the role of differential DNA methylation in post-amputation pain syndromes and their treatment with valproate.

Identify priority pathways through metabolomics pathways, analyze DNA methylation patterns associated with chronic pain phenotypes and correlate with gene expression patterns.

- | | |
|--|----------|
| a. Discovery Metabolomic analysis of 10 controls, 10 severe pain phenotype at 2 timepoints
Analysis of samples from day 0 and 90 (40 samples) | Month 28 |
| b. Methylation analysis performed on 20 control and 20 severe pain patients
Analysis of samples from day 0, 7 and 90 (120 samples) | Month 28 |
| c. Genome-wide gene expression analysis performed on 20 control and 20 severe pain patients to confirm relevance of differential methylation.
(120 samples) | Month 28 |

<u>Milestone</u> Task 3a –Pathway prioritization focusing on cytokines and inflammation, neuronal signal transduction and pain-related neuronal transmission.	Month 31
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<u>Milestone</u> Task 3b – Initial methylation data complete	Month 32
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<u>Milestone</u> Task 3c – Initial gene expression data obtained	Month 32
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- | | |
|--|----------|
| d. Validation Metabolomics performed on 10 controls, 10 severe pain at 2 time points
Analysis of samples from day 0 and 90 (40 samples) | Month 36 |
| e. Methylation analysis performed on additional 20 controls, 20 severe pain phenotypes
Analysis of samples from day 0, 7, and 90 (120 samples) | Month 36 |
| f. Genome-wide gene expression analysis performed on 20 control and 20 severe pain patients to confirm relevance of differential methylation.
(120 samples) | Month 36 |

<u>Milestone</u> Task 3d,3e,3f – Validation of initial pathway discovery using unbiased Metabolomics, genome wide methylation analysis, and gene expression	Month 38
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- | | |
|--|----------|
| g. Targeted methylation analysis using EpiTect methylation arrays. 50 patients (150 samples) | Month 40 |
| h. Targeted gene expression analysis of 50 patients using RT-PCR (150 samples) | Month 40 |

<u>Milestone</u> Task 3g,3h – Targeted analysis of methylation status at promoter regions of genes of interest with confirmatory gene expression analysis using RT-PCR	Month 40
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<u>Final Task 3 Milestone</u> – Local investigator meeting for convergence analysis of	Month 46
--	----------

metabolomics, epigenetic and gene expression data.

Timeline

4) Task 4 – Reports

- | | |
|---|--------------|
| a. Annual Progress Report, Year 1 | Month 13 |
| b. Annual Progress Report, Year 2 | Month 25 |
| c. Annual Progress Report, Year 3 | Month 37 |
| d. Final Summary Report, Year 4 | Month 49 |
| e. Manuscript 1 Submission – Initial Metabolomic Data | Months 35-37 |
| f. Manuscript 2 Submission – Initial Epigenetic and Methylation Data | Months 35-37 |
| g. Manuscript 3 Submission: Effect of valproate on incidence of chronic pain after amputation. | Months 48-49 |
| h. Manuscript 4 Submission: Epigenetic modifications in chronic pain. | Month 50 |
| i. Manuscript 5 Submission: Convergence data for metabolic pathways, epigenetic modifications and gene expression alterations in the development of the chronic pain phenotype following amputation and nerve injury. | Months 50-51 |

Summary of Study Procedures

Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain Thomas Buchheit, PI

Study Procedures	Baseline Pre-op Clinic	Day of Surgery	Post-Op Day 1	Post-Op Days 2-6	Post-Op Day 7	Follow-up Visit 1 month	Follow-up Visit 3 months	Follow-up Visit 6 months
Screening	X							
Informed consent	X							
Study Enrollment	X							
Randomization	X							
Symptom Questionnaires	X					X	X	X
General Questionnaires	X							
Defense Veterans Pain Rating Scale	X	X	X	X	X	X	X	X
Study drug administered		X	X	X	X			
Sedation Scale	X	X	X	X	X			
Amputation Questionnaires						X	X	X
Physical exam	X					X	X	X
Blood sample (RNA, DNA)		X			X		X	
Blood sample (CBC, Liver panel)					X		X	
Endpoint adjudication							X	

Projected Quarterly Enrollment

	Year 1				Year 2				Year 3				Year 4				Total
Target Enrollment (per quarter)	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Durham VAMC*	-	-	-	-	2	2	4	2	2	5	7	6	7	6	7	5	55
Duke University Medical Center	-	-	-	-	-	-	-	3	11	25	26	22	22	22	22	2	155
WRNMMC**	-	-	-	-	-	0	3	3	20	20	20	20	20	20	20	20	166
Target Enrollment (cumulative)	-	-	-	-	2	2	7	8	33	50	53	48	49	48	49	30	376

With our enrollment goal of 420 and enrollment start date in Year 2, Quarters 1, we will likely request an Extension Without Funds (EWOFF) in the latter part of Year 4 in order to complete our enrollment goal.

Blue shading = actual

Green shading = projected

*VAMC – Veterans Administration Medical Center

**WRNMMC – Walter Reed National Military Medical Center

Buchheit, W81XWH-12-2-0129, 6.25 2014	9/30/2012 - 9/29/2013		9/30/2013 - 9/29/2014		7/1/2014 - 9/29/2014		9/30/2014 - 9/29/2015		9/30/2015 - 9/29/2016	
PERSONNEL	year 1		year 2		Yr 2, Qtr 4		year 3		year 4	
	effort	sal + fringe	effort	sal + fringe			effort	sal + fringe	effort	sal + fringe
Buchheit, PI	25%	32,610	25%	32,610	na	na	25%	32,610	25%	32,610
Shaw, Co-I	10%	10,056	10%	6,704	10%	0	10%	0	10%	0
David MacLeod, Investigator					40%	2,514	40%	10,056	40%	10,056
John Hsia, Investigator			88 3%	45,785	36%	6,222	36%	24,889	36%	24,889
Thomas Van de Ven, Investigator					37%	6,428	37%	25,713	37%	25,713
Yi-Ju Li, Investigator							11.5%	20,322	11.5%	20,322
Xue J Qin, Biostatistician III							23.0%	22,680	23.0%	23,136
William White, Statistician	0%	0	9%	12,768			9%	13,343	12.0%	17,711
Mary Kirkley, Project Manager	100%	60,965	50%	31,397			50%	32,986	50%	33,646
Dionne Apedjhou, CRCII	75%	58,451	100%	80,272			100%	82,680	100%	85,160
Magdi Elgasim					25%	4,787	25%	19,530	25%	20,116
G. ego y, Co-I	10%	14,242	10%	14,669				0		0
Lan Lan, Co-I	10%	12,354								
Joshua Beaver, Research Assistant II	25%	10,732	25%	11,054				0		0
		199,410		235,258		19,951		284,809		293,359
										1,032,786

EQUIPMENT		
Multi-channel SOLO Robotic Pipettor	28,000.00	28,000 00

SUPPLIES AND MATERIALS (645000)				
Study Ascertainment/processing/shipping (breakout below				
Patient files (420), s59704, 25bx@\$71.20/ea x 17bx = \$121	0 00	404.00	403.48	
copy paper (5pt/ream) s813903, 9bx@\$60=\$540	49 00	180.00	180.00	
81 ct cryo box, 71001-642, 420x\$2.13ea=\$894.60	298 20	298.20	298.20	
64 ct PAXgene cryo box, 89128-178, 210x\$2.35ea=\$493.50	165 00	165.00	165.00	
BDVacutainer SafetyLok Collection Set, 89005-532, 3csx26	262 00	262.00	262.00	
Pipettes, 7ml, 14235-158, 2pks	45 02			
powder-free latex gloves, XL 82026-430, 4cs@\$110.03 = \$4	110 03	110.03	110.03	110.03
barcoded tube labels, 25/pt, 1000/rl, 12rl x \$325=\$3,900	975 00	975.00	975.00	975.00
95kPa bags, 89170-954, 250/cs, 1cs@\$705	176 25	176.25	176.25	176.25
Lg Insulated Shipper Box, 15713-545, 6pt/box, 3bx/cs, 14cs	315 28	315.28	315.28	
Plastic bags for kits, 3/pt, 11215-682, 1cs@108.23	36 07	36.07	36.07	
Barcode scanner, Uline LS2208	207 00			
Labels, Perishable, 89050-582	28 26			
Keep frozen, 89050-574	28 26			
UN3373 label, 89050-624	28 26			
UN1845 label, 82031-432	35 00			
Patient file labels, 4rl @ \$9ea, S9629	35 00			
Return address labels, 1rl	36 00			
Shipping labels, 1rl	14 00			
VWR rack 10mm holes shaking	82			
VWR rack microtubes 1.5ml shaking	82			
20ul clear pre-sterilized pipet tips/Hudson, 1cs, 50 racks, 9	385 00			
	3,392	2,922	2,921	1,261 10,496
PUBLICATION COSTS	0	0	1,500	1,500 3,000

METABOLOMIC EXPERIMENTS 40 pts/2 timepoints - \$45 277				
Metabolon \$550/pt x 80 samples = \$44,000		22,000	22,000	
EDTA 6.0 mL tube, BD367899 (3/pt .28/ea)		118	118	118
1.8mL cryovial, pink, 500/cs, 9cs@\$103ea, 9 per pt		308	308	308
	0	22,426	22,426	426 45,277
EPIGENETIC (DNA Methylation) EXPERIMENTS 80pts/3timepoints - \$87 080				
DNA Methylation, \$292 85 per sample as quoted \$70,28		35,142	35,142	
PAXgene DNA tubes, Q761115, 3 tubes/pt, 100/cs, 12cs	875	876		
PAXgene blood DNA kit Q761133 - 3 kits/pt, 25kits/bx, 5	5,015	5,015	5,015	
	5,890	41,033	40,157	0 87,080

GENE EXPRESSION EXPERIMENTS 80pts/3timepoints - \$113 187			
Globin reduction kit, 20reactions@\$338, 270 reactions; 14kits@\$338=\$4,732	2,366	2,366	

240 samples x \$230=\$55,200, processing total RNA	27,600	27,600		
240 x \$135=\$32,400, per array	16,200	16,200		
22 chips x \$20=\$440 set up fee	220	220		
240 x \$9=\$2,160 for RNA QC	1,080	1,080		
PAXgene RNA tubes 2.5mL, 77776-026, 100/cs, 9cs@\$8:	1,845	1,845	1,845	
PAXgene blood RNA kit - 3/pt, 50/cs, 25cs@\$435	3,625	3,625	3,625	
	5,470	52,936	52,936	1,845
				<u><u>113,187</u></u>

RT-PCR EXPERIMENTS 50pts/3timepoints - \$13 796 (\$32.87/pt)

DNA oligo primers, IDT 50@\$53.05=\$2,652 50				2,653
Primers - SYBR green dyes, 150 samples, 50@\$1,757x6=\$10,542				10,542
Superscript II Reverse Transcriptase, 2@300				602
				13,796
				<u><u>13,796</u></u>

EpiTect Methylation Arrays 50pts/3timepoints - \$30 504 (\$72.63/pt)

Arrays, 24/bx@\$2791; 150 samples, 6bx*\$2791=\$16,746	8,373	8,373		
Restriction enzymes, 12/bx@\$268; 150 samples, 12bx*\$268=\$3,216	1,608	1,608		
SYBR green mastermix, 24samples@\$1,757; 150 samples, 6*\$1,757=\$10,542	5,271	5,271		
	15,252	15,252		30,504
				<u><u>30,504</u></u>

OTHER EXPENSES

8-channel SOLO pipet assembly	2,520			
Digital shaking water bath (675700)	2,149			
VWR tray shaking universal 12L	228			
Pipetman, F167300 starter kit	904			
L-5 Liquid Dewar, 1.3gal, 55709-234	622			
VWR cryo access pour spout L5	190			
FreezerPro LIMS software				
RedCap Usage (696200)	284	284	284	284
Fedex service (shipping kits to/from WR) (693600)	720	720	720	720
Experimental Patient Payment (\$50 x 210) (622500)	2,600	2,650	2,600	2,650
	10,217	3,654	3,604	3,654
				<u><u>21,129</u></u>

MAINTENANCE CONTRACTS (686100)

	0	6,000	6,000	6,000
				<u><u>18,000</u></u>

TRAVEL (698600)

Program Review	1,800	1,800	1,800	1,800
DoD sponsored mtg	0	0	1,800	0
Yearly Investigator Conference	3,500	3,500	3,500	3,500
	5,300	5,300	7,100	5,300

DUKE IDS FEES	YR 2	YR 3	YR 4	
	9/30/13-9/29/14	9/30/14-9/29/15	9/30/15-9/29/16	
IDS setup fee	1350			
IDS monthly maint fee	201	804	804	
IDS closeout fee			300	
Per Subject Fees (155)	3mo	12mo	6mo	
Dispensing/Prep (\$15)	333	1332	666	
VPA (\$7)	156	624	312	
Cherry Syrup (\$11)	243	972	486	
Addtn'l blood collection supplies				
Est - \$2.01/per patient x 155 patients = \$312	45	178	89	
	2,327.57	3,910.29	2,657.14	8,895.00

TTL DIRECT COSTS	257,679	407,059	440,615	329,798	1,435,151
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adjusted DC	229,679				
IDC	130,917	232,024	251,151	187,985	802,076
	388,596	639,082	691,765	517,783	<u><u>2,237,227</u></u>

MEMORANDUM

Department of
Veterans Affairs


1st Notice

Date: August 25, 2014

SEP 25 '14 @ 10:36

From: Chairman, Institutional Review Board (151)


Subj: Human Studies Continuation Review

To: _____ Buchheit, Thomas F., M.D. , Principal Investigator

1. This to notify you that approval of your study will expire on 11/13/2014.
2. If you choose to submit the continuation review forms early, the submission must be received by the IRB agenda items due date: N/A.
3. If you submit at the normally scheduled time, the submission must be received by the IRB agenda items due date: 9/22/14.
4. Your submission, and your response to any additional IRB recommendations, must be approved by the expiration date. If your approval expires, no further study activities may be conducted until the IRB restores approval.
5. Please review the submission package for completeness and accuracy to avoid contingent approval by the IRB. Check **all applicable** boxes on the submission form and ensure that all documents are signed where required. Unless noted otherwise, all forms may be found at S:\Research Forms Jan 09\HUMAN FORMS Dec 08\Continuation Review Forms and www.durham.va.gov/research/continuing_review/Continuing_Review.asp
6. A completed continuation review submission consists of the following documents:
 - Continuation Review Form: Address each item as applicable.
 - Appendix G Certification: Item 2 is **YES** if there are no biological hazards)
 - Project Data Sheet (Attached. Review and initial any changes, i.e. Funding Source.)
 - Staff Listing: Include current training for all staff involved with the research and identify individuals serving as investigators.
 - Include the latest approved Informed Consent form (with approval stamp) and HIPAA authorization if recruitment is ongoing.
 - Include a copy of the new Conflict of Interest form for PI and all Investigators on the study. VA mandate requires this to be submitted annually.
7. The VA has mandated that human studies education/training (CITI) be completed every two years. Only current training is acceptable for renewal of studies. Studies will not be renewed for Investigators who have not updated their required training. In the event your research staff has not completed their required training, you will receive notification that they may no longer participate on your research studies.
8. If you have questions, please contact the Research Office at 286-6926 or extensions 7342 and 5170.

INTEROFFICE MEMORANDUM

TO: CHAIR, IRB

FROM: THOMAS BUCHHEIT, MD 

SUBJECT: CONTINUING REVIEW SUBMISSION FOR DVAMC IRB PROTOCOL NO. 01709: "REGIONAL ANESTHESIA AND VALPROATE SODIUM FOR THE PREVENTION OF CHRONIC POST-AMPUTATION PAIN"

DATE: SEPTEMBER 19, 2014

Thank you for reviewing our submission for Human Studies Continuation Review of the above-referenced Protocol. As directed in please find attached:

- 1) Acknowledged Memorandum of Notification of study expiration
- 2) Original Project Data Sheet (Dr. Andrew Shaw's name removed as Co-Principal Investigator)
- 3) Continuation Review Form, Pages 1-8
- 4) Copies of SAE reports from IRB, along with AE log and Deviation log
- 5) Continuation Review Form, Page 5 (Appendix G Certification) form
- 6) SOP for Research Using Human Blood, Tissue or Cell Lines with copy of staff certification
- 7) SOP for Research Transporting and Shipping Biological Specimen with copies of staff certification
- 8) Current Research Staff Listing with current training dates
- 9) Clean copy of the latest approved VA Informed Consent Form using the updated June 2014 template (consent version retained) along with a copy of the previously approved ICF.
- 10) Clean copy of HIPAA Authorization for Release of PHI using the updated template (June 2014) along with a copy of the previously approved HIPAA authorization form.
- 11) Clean copy of the latest approved Flyer for study (in color)
- 12) Clean Copy of the Abbreviated Mini Mental State Exam
- 13) Duke's IRB Personal Data Disclosure form version 7-31-2012 to be stamped (used for subject compensation)
- 14) COI Survey x 7

SEP 25 '14 AM 10:36

SEP 25 '14 AM 10:36

4. Project Title: Regional Anesthesia and Valproate Sodium for Prevention of Chronic Post-Amputation Pain

11. Status of PI in Project: 01 _____ (01 = Awardee or Initiator 02 = Not Awardee; Responsible VA Investigator)

Shaw, Andrew / M.D.	ADSHAW	558
Last name, first name, mi, degree	CID	VAMC
Last name, first name, mi, degree	CID	VAMC

<u>Source Code</u> <i>(4-digits)</i>	<u>Source Name</u>	<u>Admin Code</u> <i>(2-digits)</i>	<u>Admin Name</u>
9203	Dept of Defense	07	Affiliated University

Human Subjects ☒ Yes ☐ No Exempt ☐ Yes ☒ No
Invest Drugs ☐ Yes ☒ No IND No. _____
Invest Device ☐ Yes ☒ No IDE No. _____
Animal Subjects ☐ Yes ☒ No Radioisotopes ☐ Yes ☒ No Biohazards ☒ Yes ☐ No

CRADO Approval Date: N/A

1) PAIN _____ 4) _____

2) NERVE _____ 5) _____

3) AMPUTATION _____ 6) _____

1) _____ 2) _____ 3) _____ 4) _____
5) _____ 6) _____ 7) _____ 8) _____
9) _____ 10) _____ 11) _____ 12) _____
13) _____ 14) _____ 15) _____ 16) _____

Durham VAMC: Request for Continuing Review of Research

Principal Investigator: Thomas Buchheit, MD	MIRB #: 01709
Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain	Date: 08/20/2014
[Research Office Use Only] Continuing Review Approved: _____ until: _____	

SEP 25 14 41037

A. Study Status at the Durham VAMC: Please choose a response that best describes your study status. If none are applicable, check "other" and explain.

<input type="checkbox"/>	Retrospective chart review or study of existing data/specimens:	<input type="checkbox"/> No new charts or specimens being reviewed/analyzed <input type="checkbox"/> Continuing to review charts or specimens
<input type="checkbox"/>	Prospective recruitment/enrollment has not started	
<input checked="" type="checkbox"/>	Open to prospective recruitment/enrollment:	<input checked="" type="checkbox"/> Active: Participants enrolled and/or randomized and/or undergoing interventions <input type="checkbox"/> No participants enrolled and/or randomized
<input type="checkbox"/>	Closed to prospective enrollment:	<input type="checkbox"/> Participants undergoing interventions <input type="checkbox"/> Participants in follow-up <input type="checkbox"/> Data analysis only
<input type="checkbox"/>	Recruitment-only (e.g., study procedures conducted at Duke or UNC, etc.)	
<input type="checkbox"/>	Study completed: Close administrative files	
<input type="checkbox"/>	Other, explain:	

B. Research Procedures: Identify applicable experimental procedures in the study.

a.	<input type="checkbox"/> FDA-monitored treatment (IND or device) If yes, provide IND/IDE #:
b.	<input type="checkbox"/> FDA-exempted drug or device (for minimal risk device check "k" below)
c.	<input checked="" type="checkbox"/> Novel combination of FDA-approved drugs or approved drug administered in novel context
d.	<input type="checkbox"/> FDA-approved drug administered in accepted clinical context
e.	<input type="checkbox"/> Surgical procedure (if any surgical component altered for research purposes)
f.	<input checked="" type="checkbox"/> Other invasive procedure (e.g., x-ray, anesthesia or arterial blood draw)
g.	<input checked="" type="checkbox"/> Venous blood draw
h.	<input type="checkbox"/> Benign prospective collection of specimens (through swab, fluid collection, etc.)
i.	<input type="checkbox"/> Behavioral medicine intervention (including exercise, diet, or sleep modification)
j.	<input type="checkbox"/> Experimental behavioral interaction with participant (e.g., psychotherapy)
k.	<input type="checkbox"/> Data from imaging or minimal risk device (if X-ray or radiologic agent used, check 'f' above)
l.	<input checked="" type="checkbox"/> Observation or measurement of behavior (survey, cognitive testing, functional evaluation)
m.	<input type="checkbox"/> No participant interaction; data obtained from existing specimens, recordings or databases
n.	<input checked="" type="checkbox"/> Other: In 'l' above, an abbreviated Mini Mental Health Status Examination is administered prior to consenting a participant to ascertain a level of cognition; additionally a PHQ2 (Depression Screening Questionnaire) is administered after Informed consent is obtained along with a number of surveys related to pain and amputation status. During Study Drug Administration, a Richmond Agitation Sedation Scale is used to assess the patients during

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD

MIRB: 01709

v.2014-06-12

Page 2 of 8

B. Research Procedures: Identify applicable experimental procedures in the study.

hospitalization.

C. Risks

1. Indicate risk level: ☐ Minimal risk ☒ Greater than minimal risk

2. Are there any special privacy risks? ☐ N/A

☒ Genetic analysis ☐ Voice/image recording ☐ Social/financial risk

D. Participant Information

1. Are non-Veterans enrolled in this study? ☐ Yes ☒ No

2. As applicable, indicate the number of participants and/or records and/or specimens entered for the review period and since the inception of the study. Also provide information on withdrawals during this review period.

Enrollment Type		Prior enrollment	During this review period
<input checked="" type="checkbox"/>	Number of participants enrolled:	0	9
	Number of participants withdrawn:	0	1
	Number withdrawn during this review period: a. Lost to follow-up: b. Clinical/Safety reasons: c. Non-adherence to protocol: d. Participant died: e. Ineligibility: f. Other: 1 <i>(Study team unable to treat patient with Investigational agent who was added unto surgical schedule at the last minute during the snow storm/black ice in February 2014 when only essential hospital staff was on site.)</i>		

For Retrospective Studies:

<input type="checkbox"/>	Number records enrolled:		
	Number of records withdrawn:		
	If applicable, reason(s) for withdrawal(s):		

<input type="checkbox"/>	Number specimens enrolled:		
	Number of specimens withdrawn:		
	If applicable, reason(s) for withdrawal(s):		

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	v.2014-06-12	Page 3 of 8
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D. Participant Information

3. Enter the cumulative participant gender and minority status for the Durham site only.

☐ The study enrolled human subjects but gender and minority status were not collected.

2a. Race	Females	Males	Sex/Gender unknown or not reported	Total
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	4	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0
White	0	5	0	5
More than one race	0	0	0	0
Unknown or not reported	0	0	0	0

2b. Ethnicity	Females	Males	Sex/Gender unknown or not reported	Total
Hispanic or Latino	0	0	0	0
Not Hispanic or Latino	0	9	0	9
Unknown or not reported	0	0	0	0

*The Ethnic Categories total must equal the Racial Categories total.

4. Number of participants considered to be members of specific vulnerable populations:

	Females	Males	Sex/Gender Unknown or not reported	Total
Pregnant women	0	n/a	0	0
Prisoners	0	0	0	0
Children	0	0	0	0
Subjects who lack decision making capacity	0	0	0	0

5. Do you make a reasonable effort to provide the "Volunteering in Research" brochure in settings where subjects may be recruited (e.g., clinic areas)? ☒ Yes ☐ No ☐ N/A

6. Do you make a reasonable effort to provide the "Volunteering in Research" brochure to each prospective subject when that individual is approached to take part in the study?

☒ Yes ☐ No ☐ N/A

E. Informed Consent and HIPAA Authorization

	Yes	No
1. Does this study have waivers of informed consent and HIPAA authorization to screen and recruit?	<input checked="" type="checkbox"/>	<input type="checkbox"/>
2. What type of informed consent was used?		

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	v.2014-06-12	Page 4 of 8
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E. Informed Consent and HIPAA Authorization	Yes	No
<input checked="" type="checkbox"/> Written consent form <input type="checkbox"/> Waiver of documentation of informed consent <input type="checkbox"/> None: Waiver of informed consent		
3. If applicable, include the currently approved ICF. <input type="checkbox"/> Not applicable		
4. Were all participants enrolled at Durham entered on a master list of subjects after signing and dating the approved ICF prior to undergoing any study interactions or interventions? <input type="checkbox"/> Not applicable: The IRB granted a waiver of informed consent or a waiver of documentation of informed consent	<input checked="" type="checkbox"/>	<input type="checkbox"/>
5. What type of HIPAA authorization was used? <input checked="" type="checkbox"/> Written HIPAA authorization <input type="checkbox"/> None: Waiver of HIPAA authorization		
6. If applicable, include the currently approved HIPAA authorization. <input type="checkbox"/> Not applicable		

F. Amendments									
1. Provide a list of all amendments to the protocol since last IRB initial or continuing review, whichever is most recent. If more space is needed, attach additional page(s) as necessary. <input type="checkbox"/> There have been no amendments since the last IRB review.									
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: center; padding: 5px;">Amendment Approval Date</th> <th style="text-align: left; padding: 5px;">Brief Description of Amendment</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; padding: 5px;">12/12/2013</td> <td style="padding: 5px;">Amendment included administrative changes to version 27 of the study protocol, Informed Consent Form, HIPAA Authorization Form, addition of new Research Coordinator to the HIPAA Waiver, telephone scripts for review, amended VA Form-10-9012 and update of the processing of compensation to study participants.</td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> <tr> <td style="height: 20px;"></td> <td></td> </tr> </tbody> </table>	Amendment Approval Date	Brief Description of Amendment	12/12/2013	Amendment included administrative changes to version 27 of the study protocol, Informed Consent Form, HIPAA Authorization Form, addition of new Research Coordinator to the HIPAA Waiver, telephone scripts for review, amended VA Form-10-9012 and update of the processing of compensation to study participants.					
Amendment Approval Date	Brief Description of Amendment								
12/12/2013	Amendment included administrative changes to version 27 of the study protocol, Informed Consent Form, HIPAA Authorization Form, addition of new Research Coordinator to the HIPAA Waiver, telephone scripts for review, amended VA Form-10-9012 and update of the processing of compensation to study participants.								

G. Data Safety Monitoring and Risk / Benefit Assessment	Yes	No	N/A
1. Have there been any adverse events (AEs) in this review period? <i>If yes, attach a summary/list of all AEs that have occurred during the review period.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Have there been any Serious Adverse Events (SAEs) in this review period? <i>If yes, attach a summary/list of all AEs that have occurred during the review</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	v.2014-06-12	Page 5 of 8
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G. Data Safety Monitoring and Risk / Benefit Assessment	Yes	No	N/A
period. <input type="checkbox"/> SAEs that did not have to be reported within 5 business days are attached. <input checked="" type="checkbox"/> All local unanticipated SAEs (whether related or unrelated to the research) that required 5-business day reporting have already been submitted to the IRB.			
3. Have there been any unanticipated problems involving risks to subjects or others during the review period? <i>If yes, attach a summary/list of all unanticipated problems that have occurred during the review period.</i> <input type="checkbox"/> Unanticipated problems that did not have to be reported within 5 business days are attached. <input type="checkbox"/> All local unanticipated problems that required 5-business day reporting have already been submitted to the IRB.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4. Have there been any protocol or policy deviations during this review period? <i>If yes, attach a summary/list of all deviations.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Have there been any summaries, recommendations, or minutes from DMC/DSMB meetings or findings based on information collected by the data and safety monitoring plan? <i>If yes, submit with continuing review package.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6. Have there been any subject claims of injury or complaints regarding the research since the last Continuing Review and/or Initial Review? <i>If yes, describe:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

H. Is this study part of a multi-center research project?	Yes	No
<i>If yes:</i> 1. Durham is the lead site & other sites' IRB initial approvals were/will be submitted. 2. If available, relevant multi-center trial report(s) are attached. <input type="checkbox"/> N/A	<input checked="" type="checkbox"/>	<input type="checkbox"/>

I. Conflict of Interest	Yes	No
1. I have attached Conflict of Interest statements for all Investigators.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

J. Overview / Findings
1. Please provide a brief summary of the research (include methodology). This study is a prospective, randomized double blind phase II trial of VPA for amputation, stump revision surgery or surgery to limb with neurological damage. Patients will be randomized on a sequential basis. 420 patients will be enrolled over a 4 years duration at the 2 sites. The Durham

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	v.2014-06-12	Page 5 of 8
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G. Data Safety Monitoring and Risk / Benefit Assessment	Yes	No	N/A
period.			
<input type="checkbox"/> SAEs that did not have to be reported within 5 business days are attached. <input checked="" type="checkbox"/> All local unanticipated SAEs (whether related or unrelated to the research) that required 5-business day reporting have already been submitted to the IRB.			
3. Have there been any unanticipated problems involving risks to subjects or others during the review period? <i>If yes, attach a summary/list of all unanticipated problems that have occurred during the review period.</i> <input type="checkbox"/> Unanticipated problems that did not have to be reported within 5 business days are attached. <input type="checkbox"/> All local unanticipated problems that required 5-business day reporting have already been submitted to the IRB.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
4. Have there been any protocol or policy deviations during this review period? <i>If yes, attach a summary/list of all deviations.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Have there been any summaries, recommendations, or minutes from DMC/DSMB meetings or findings based on information collected by the data and safety monitoring plan? <i>If yes, submit with continuing review package.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
6. Have there been any subject claims of injury or complaints regarding the research since the last Continuing Review and/or Initial Review? <i>If yes, describe:</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

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<i>If yes:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
1. Durham is the lead site & other sites' IRB initial approvals were/will be submitted.	<input type="checkbox"/>	<input type="checkbox"/>
2. If available, relevant multi-center trial report(s) are attached. <input type="checkbox"/> N/A	<input checked="" type="checkbox"/>	<input type="checkbox"/>

I. Conflict of Interest	Yes	No
1. I have attached Conflict of Interest statements for all Investigators.	<input checked="" type="checkbox"/>	<input type="checkbox"/>

J. Overview / Findings
1. Please provide a brief summary of the research (include methodology). This study is a prospective, randomized double blind phase II trial of VPA for amputation, stump revision surgery or surgery to limb with neurological damage. Patients will be randomized on a sequential basis. 420 patients will be enrolled over a 4 years duration at the 2 sites. The Durham

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD

MIRB: 01709

v.2014-06-12

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J. Overview / Findings

VA Medical Center and Duke University Medical Center will be considered a single site and is referred to as the Durham Site or DVAMC/DUMC. 420 patients (210 patients at Duke University Medical Center/Durham VAMC (DUMC/DVAMC) and 210 at Walter Reed National Military Medical Center) will be enrolled. Of the 210 patients, 105 patients will be randomized to placebo, and 105 patients will be randomized to receive every 8 hour doses of placebo/VPA 250mg for a total of 21 doses over 7 days or until the time of discharge from the hospital, if discharged before 7 days. Patients will receive all 21 doses of study drug unless they withdraw their consent, are discharged prior to post-op day 6, or either their treating physician or the principal investigator believes it would be dangerous to continue valproate.

"Control" patients will receive standard regional anesthesia catheters (either peripheral nerve or epidural catheter), anesthetic management and a placebo. "Intervention arm" patients will receive standard regional anesthesia catheters (either peripheral nerve or epidural catheter), anesthetic management, and valproic acid 250mg preoperatively, and then three times per day for 6 days post-operatively or until of discharge from the hospital if before 7 days. Given the pragmatic nature of this trial, there will be no washout period prior to starting the medication and patients will continue to take their standard perioperative medications.

Subjects will be recruited from the surgical clinics and the anesthesia pre-operative clinic. After screening and enrollment, the study medication (VPA or placebo) will be administered for a total of 7 days (day of surgery and 6 days following surgery) or until the time of discharge from the . Longitudinal follow-up will occur in the Pain Clinic that is managed by the principal investigator. Outcomes for patients in the intervention arm will be compared with those managed with the current institutional standards of care including regional anesthesia catheter infusions.

Research blood samples will be collected preoperatively, postoperatively (at the completion of study drug intervention), and at Pain Clinic follow-up (approximately 3 months) for analysis of metabolic changes, epigenetic modifications, and gene expression alterations. All samples will be de-identified and subsequently studied in our laboratory in the Snyderman Genome Sciences Research Building and several core facilities at Duke. We will also use a 3rd party metabolomics facility, Metabolon, Inc. in Raleigh, to measure plasma metabolomic differences between case and control subjects. Metabolon will receive completely de-identified plasma samples for these assays. Quest Diagnostics will receive de-identified samples of serum for analysis of VPA levels obtained at the end of study drug administration.

2. If available, provide research findings to date. ☒ N/A

3. If available, provide new scientific findings in the literature, or other relevant findings, that may impact the research. ☒ N/A

4. Have there been any study publications since the last and/or initial review? ☐ Yes ☒ No
If yes, attach the publication(s) with this submission.

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD

MIRB: 01709

v.2014-06-12


Page 7 of 8

J. Overview / Findings

5. If applicable, was the VA acknowledged in each publication? ☐ N/A ☐ Yes ☒ No

☒ **Considering all of the above, the risks in this project are still outweighed by the benefits.**

VERIFICATION: I am aware that all research projects using human subjects must receive prior approval by the IRB, that any change in this project requires prior approval by the IRB, that consent must be obtained from each subject before entry into the study unless waived, that continuing review is required at least once annually, that projects using human subjects not receiving favorable review must be discontinued, and that a copy of all consent forms (as applicable) and study-related matters must be retained by the Principal Investigator according to VA policy.


Principal Investigator Signature


Date

FOR RESEARCH OFFICE USE ONLY:

<input type="checkbox"/> Approve <input type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
IRB Member Signature:	Date:

<input type="checkbox"/> Approve <input type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
SRS Member Signature: (<input type="checkbox"/> Not Applicable)	Date:

<input type="checkbox"/> Approve <input type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
R&DC Member Signature: (<input type="checkbox"/> Not Applicable)	Date:

Durham VAMC: Request for Continuing Review of Research

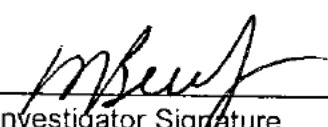
Investigator: Thomas Buchheit, MD	MIRB: 01709	v.2014-06-12	Page 7 of 8
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J. Overview / Findings

5. If applicable, was the VA acknowledged in each publication? ☐ N/A ☐ Yes ☒ No

☒ **Considering all of the above, the risks in this project are still outweighed by the benefits.**

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Principal Investigator Signature


Date

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Comments:	
IRB Member Signature:	Date:

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Comments:	
SRS Member Signature: (<input type="checkbox"/> Not Applicable)	Date:

<input type="checkbox"/> Approve <input type="checkbox"/> Contingent Approval <input type="checkbox"/> Disapprove <input type="checkbox"/> Table	
Comments:	
R&DC Member Signature: (<input type="checkbox"/> Not Applicable)	Date:

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	Page 8 of 8
Study Title: of Chronic Post-Amputation Pain		v.2014-06-12

FOR IRB USE ONLY

Date:

You are reminded that no changes or modifications may be implemented for this study, except where necessary to eliminate apparent immediate hazards to participants, until you have requested and received full approval from all applicable subcommittees.

You are also reminded that all study personnel with a Durham VAMC appointment (e.g., VA-paid, WOC, or IPA) must remain current with all applicable research training and must maintain a current Research Scope of Practice.

No research may be continued beyond the designated approval period.

Sincerely,

John D. Whited, MD, MHS
Associate Chief of Staff for Research and Development

Durham VAMC: Request for Continuing Review of Research

Investigator: Thomas Buchheit, MD	MIRB: 01709	Page 8 of 8
Study Title: of Chronic Post-Amputation Pain		v.2014-06-12

FOR IRB USE ONLY

Date:

You are reminded that no changes or modifications may be implemented for this study, except where necessary to eliminate apparent immediate hazards to participants, until you have requested and received full approval from all applicable subcommittees.

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No research may be continued beyond the designated approval period.

Sincerely,

John D. Whited, MD, MHS
Associate Chief of Staff for Research and Development

Durham Veterans Affairs Medical Center
Institutional Review Board

Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

Instructions: Complete this form for any local Serious Unanticipated Problem or local Unanticipated Serious Adverse Event. Report the Problem/Event within 5 business days of Study Staff/Principal Investigator becoming aware of Problem/Event. Problems/events that do not meet the 5 business day reporting requirement should be reported at continuing review per local SOPs.

Principal Investigator: Thomas Buchheit, MD	Study Coordinator: Dionne Apedjihoun
Title of Protocol: Regional Anesthesia and Valproate Sodium for the prevention of Chronic Post-Amputation Pain	
MIRB Number: 01709	Participant Study ID (no SSN): 127647
Date of Event: 06/08/2014	Date Notified of Event: 7/11/2014

- ☒ Durham VAMC Study Event (Local)
☐ Sponsor/Off-site Event (Submit only if meaningful analysis is provided, attach report to this form)

Description of Event: SIRS (systemic inflammatory response syndrome) secondary to Cellulitis

Study Participant 127647 was enrolled onto the above-referenced Clinical Trial on April 28, 2014 with a left nonhealing BKA (below knee amputation) with secondary infection; this was revised to a guillotine AKA (above knee amputation). The patient was treated on the same day with the investigational agent and also for 6 days post-op. then discharged to CLC on May 10, 2014. On May 13, 2014, the patient reported removing a scab from the right medial malleolus; the right 2nd toe had an abraded area from a friction/scrape injury. These wounds were continuously evaluated in CLC and were noted to have improved. The patient was taught to dress the wounds and was discharged to home from CLC on May 24, 2014 with amputated limb in steri strips and improved wounds of the right foot and inner ankle.

On evaluating the patient's progress via CPRS, the Greenville's Clinical Pharmacist noted July 10, 2014 that the study patient was found driving his car in a confused state around the parking lot of Wayne Memorial Hospital on June 8, 2014. He was admitted to the ED for altered mental status. On examination and evaluation the patient was found to be tachycardic with a temperature of 105.2 deg.F, WBC > 21000, INR = 5.9 and Lactic acid of 31.

The patient was treated with Vitamin K for elevated INR, as well as Vanc and Zosyn for SIRS secondary to Cellulitis on the right lower extremity. Meningitis was ruled out and the patient was discharged with "Levofloxacin 500 mg PO daily, metronidazole 500 mg TID for 7 days" and advised to cease the use of warfarin. The Study Participant was instructed to follow-up with the vascular surgeon at the DVAMC in 2 weeks from the time of discharge on 6/10/2014.

Serious Adverse Event? ☐ No ☒ Yes: Check all reasons that apply:

- ☐ Death ☒ Life-threatening event ☒ Hospitalization (inpatient or prolonged)
☐ Persistent or significant disability/incapacity ☐ Congenital anomaly or birth defect
☐ Important Medical Event (an event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the other "serious" outcomes)

Serious Problem? ☐ No ☒ Yes: Check all reasons that apply:

- ☐ Interruption of subject enrollment or other research activity due to concern(s) about the safety, rights, or welfare of human research subjects, research staff, or others
☐ Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention, requires extended surveillance of the affected individuals, or leads to serious complications or death
☐ Any action taken in response to a VA Pharmacy Benefits Management (PBM) Bulletin or Communication

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Durham Veterans Affairs Medical Center
Institutional Review Board

Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

- ☐ Any action taken in response to a VA Pharmacy Benefits Management (PBM) Bulletin or Communication.
- ☐ A DMC, DSMB, or DSMC report describing a safety problem
- ☐ Sponsor analysis describing a safety problem for which action at the facility level may be warranted
(Note: Sponsor AE reports lacking meaningful analysis do not constitute "problems")
- ☐ An unanticipated problem involving substantive harm (or a genuine risk of substantive harm) to the safety, rights or welfare of human subjects, research staff, or others
- ☐ A problem reflecting a deficiency that substantively compromises the effectiveness of Durham VAMC's human research protection program
- ☐ Any protocol deviation that places one or more subjects at increased risk of harm
- ☐ Any lost or stolen electronic devices used in or for research purposes (laptops, personal digital assistants or other electronic recording devices, etc.)
- ☒ Other: Related to new injury resulting in SIRS secondary to Cellulitis

Unanticipated? ☒ Yes ☐ No: Check reasons why this event is anticipated:

- ☐ Event listed in protocol ☐ Event listed in informed consent
- ☐ Event listed in Investigator Brochure, package insert, or other product information
- ☐ Expected per study population and documented in protocol; explain:
- ☐ Other, explain:

Study related? ☒ No ☐ Yes: ☐ Definitely related ☐ Probably related

Corrective action plan, including plan to prevent recurrence: Since the SIRS was believed to be related to infection at a new site and not the study limb nor study drug/placebo and procedures, we do not believe a corrective action plan is indicated in the course of the study.

Have risks to subjects or others changed?

- ☐ Yes, please explain:
- ☒ No, please explain: N/A

Will additional information be given to enrolled subjects?

- ☒ No ☐ Yes: Please explain how and append appropriate documents:

Note: If the consent requires revisions, no new participants may be enrolled until the revised consent form has been approved.

Have you complied with all applicable reporting requirements? (e.g., of the Sponsor and/or FDA)

- ☒ Yes ☐ No ☐ Not applicable

My signature certifies the following:

- ☒ All necessary information has been assessed and is completed in sufficient detail to facilitate IRB review.
- ☒ The risks of the research are minimized to the greatest extent possible.
- ☒ The risk-benefit relationship of the research continues to be acceptable.
- ☒ The consent form does not require revision.
- ☐ The consent form requires revision. An underlined copy and a clean copy of the revised consent are attached.

Investigator Signature

Date

FOR IRB USE ONLY

IRB Reviewer Determination of Problem/Event:

Durham Veterans Affairs Medical Center
Institutional Review Board

Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

- ☒ Serious ☐ Not Serious
☒ Unanticipated ☐ Anticipated
☐ Related ☒ Unrelated

Reminder: The IRB Chair must report serious, unanticipated, and related events to the Facility Director in 5 business days.

- ☐ The consent form requires revision.
☒ The consent form does not require revision.
☐ The event should be reviewed by the convened IRB.

Reminder: This must be reported to the convened IRB, who then must determine whether or not previously enrolled subjects must be notified of the modification and, if so, when such notification must take place and how such notification must be documented.

- ☐ Immediate action (e.g., suspension, subject notification) is necessary to prevent an immediate hazard to subjects.
☐ No immediate action is warranted to prevent an immediate hazard to subjects, but convened IRB review required.
☒ The risk-benefit relationship of the research continues to be acceptable.
☐ The risk-benefit relationship of the research is not acceptable.
☐ If applicable, the additional information provided to subjects is acceptable.
☐ If applicable, the additional information provided to subjects is not acceptable.

Comments:



IRB Reviewer Signature

7/21/14
Date

INTEROFFICE MEMORANDUM

TO: CHAIR, IRB
FROM: THOMAS BUCHHEIT, MD
SUBJECT: SAE FOR PT. 127647 ON THE "REGIONAL ANESTHESIA AND VALPROATE SODIUM FOR THE PREVENTION OF CHRONIC POST-AMPUTATION PAIN" STUDY
DATE: 07/16/2014

Study Participant with ID # 127647, experienced an unexpected serious adverse event unrelated to the investigational agent on 06/08/2014; the study team was made aware on 07/11/2014. Attached is a copy of the Serious Unanticipated Problem/Serious Unanticipated Adverse Event Report Form with additional data for your review.

Durham Veterans Affairs Medical Center
Institutional Review Board
Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

Instructions: Complete this form for any local Serious Unanticipated Problem or local Unanticipated Serious Adverse Event. Report the Problem/Event within 5 business days of Study Staff/Principal Investigator becoming aware of Problem/Event. Problems/events that do not meet the 5 business day reporting requirement should be reported at continuing review per local SOPs.

Principal Investigator: Thomas Buchheit, MD	Study Coordinator: Dionne Apedjihoun
Title of Protocol: Regional Anesthesia and Valproate Sodium for the prevention of Chronic Post-Amputation Pain	
MIRB Number: 01709	Participant Study ID (no SSN): 127502
Date of Event: 4/12/2014	Date Notified of Event: 4/18/2014

- ☒ **Durham VAMC Study Event (Local)**
☐ **Sponsor/Off-site Event** (Submit only if meaningful analysis is provided, attach report to this form)

Description of Event: Acute Kidney Injury (AKI) secondary to Antibiotics

On 4/8/2014, the study participant with a history of poorly controlled Type II Diabetes Mellitus, Hyperlipidemia, Hypertension presented to the ER with fevers, malaise, dysuria and increased drainage from diabetic ulcer on foot (Rt). The patient was evaluated (labs and xrays) and creatinine was noted to be 1.2 mg/dL. Urinalysis revealed "gross pyuria and Bacituria". The patient was treated with broad broad spectrum antibiotics with vancomycin and zosyn.

The patient underwent an amputation of 1st and 2nd toe of the right foot on Friday, 4/11/2014; an Informed Consent to participate in the Research Protocol 01709 was obtained earlier in the day. The patient received the first dose of investigational agent (VPA/Placebo) on 4/11/2014 then 3 times per day every 8 hours until 4/18/2014.

The patient reported no known side-effects to the investigational agent. However, the patient's vancomycin was discontinued on 4/12/2014 due to concern for nephrotoxicity. The patient was switched to nafcillin in addition to the zosyn. On 4/14/2014 nephrology consult for AKI was requested. On 4/18/2014 an Infectious Disease consult was additionally requested for recommendation given "kidney injury with [vancomycinEmpiric]". The patients creatinine had risen from 1.2 (4/10/2014), to 1.9 (4/11/2014), to 4.2 (4/12/2014) to 5.4 (4/13/2014) to 6.7 mg/dL on 4/18/2014.

On 4/21/2014, Nephrology consult indicated that creatinine was beginning to trend downwards and was 6.4 mg/dL; it is believed that "decreased po intake and relative hypotension on 4/11" contributed to the event. As of 4/23/14, the patient's continuing to trend downward creatinine was 6.1.

Serious Adverse Event? ☐ No ☒ Yes: Check all reasons that apply:

- ☐ Death ☐ Life-threatening event ☐ Hospitalization (inpatient or prolonged)
☐ Persistent or significant disability/incapacity ☐ Congenital anomaly or birth defect
☒ Important Medical Event (an event that may jeopardize the subject and may require medical or surgical intervention to prevent one of the other "serious" outcomes)

Serious Problem? ☐ No ☒ Yes: Check all reasons that apply:

- ☐ Interruption of subject enrollment or other research activity due to concern(s) about the safety, rights, or welfare of human research subjects, research staff, or others
☐ Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention, requires extended surveillance of the affected individuals, or leads to serious complications or death

Durham Veterans Affairs Medical Center
Institutional Review Board

Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

- ☐ Any action taken in response to a VA Pharmacy Benefits Management (PBM) Bulletin or Communication
- ☐ A DMC, DSMB, or DSMC report describing a safety problem
- ☐ Sponsor analysis describing a safety problem for which action at the facility level may be warranted
(Note: Sponsor AE reports lacking meaningful analysis do not constitute "problems")
- ☐ An unanticipated problem involving substantive harm (or a genuine risk of substantive harm) to the safety, rights or welfare of human subjects, research staff, or others
- ☐ A problem reflecting a deficiency that substantively compromises the effectiveness of Durham VAMC's human research protection program
- ☐ Any protocol deviation that places one or more subjects at increased risk of harm
- ☐ Any lost or stolen electronic devices used in or for research purposes (laptops, personal digital assistants or other electronic recording devices, etc.)
- ☒ Other: Related to antibiotic management of his infection

Unanticipated? ☒ Yes ☐ No: Check reasons why this event is anticipated:

- ☐ Event listed in protocol ☐ Event listed in informed consent
- ☐ Event listed in Investigator Brochure, package insert, or other product information
- ☐ Expected per study population and documented in protocol; explain:
- ☐ Other, explain:

Study related? ☒ No ☐ Yes: ☐ Definitely related ☐ Probably related

Corrective action plan, including plan to prevent recurrence: Since the AKI was believed to be related to antibiotic toxicity in the treatment of the patient's wound, and unrelated to the study drug/placebo, we do not believe a corrective action plan is indicated in the course of the study.

Have risks to subjects or others changed?

- ☐ Yes, please explain:
- ☒ No, please explain:

Will additional information be given to enrolled subjects?

- ☒ No ☐ Yes: Please explain how and append appropriate documents:

Note: If the consent requires revisions, no new participants may be enrolled until the revised consent form has been approved.

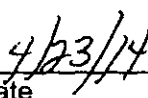
Have you complied with all applicable reporting requirements? (e.g., of the Sponsor and/or FDA)

- ☒ Yes ☐ No ☐ Not applicable

My signature certifies the following:

- ☒ All necessary information has been assessed and is completed in sufficient detail to facilitate IRB review.
- ☒ The risks of the research are minimized to the greatest extent possible.
- ☒ The risk-benefit relationship of the research continues to be acceptable.
- ☒ The consent form does not require revision.
- ☐ The consent form requires revision. An underlined copy and a clean copy of the revised consent are attached.


Investigator Signature


Date

FOR IRB USE ONLY

IRB Reviewer Determination of Problem/Event:

Durham Veterans Affairs Medical Center
Institutional Review Board

Serious Unanticipated Problem / Serious Unanticipated Adverse Event Report Form

- ☒ Serious ☐ Not Serious
☐ Unanticipated ☒ Anticipated
☐ Related ☒ Unrelated

Reminder: The IRB Chair must report serious, unanticipated, and related events to the Facility Director in 5 business days.

- ☐ The consent form requires revision. → **Reminder:** This must be reported to the convened IRB, who then must determine whether or not previously enrolled subjects must be notified of the modification and, if so, when such notification must take place and how such notification must be documented.
- ☒ The consent form does not require revision.
- ☐ The event should be reviewed by the convened IRB.
- ☐ Immediate action (e.g., suspension, subject notification) is necessary to prevent an immediate hazard to subjects.
- ☐ No immediate action is warranted to prevent an immediate hazard to subjects, but convened IRB review required.
- ☒ The risk-benefit relationship of the research continues to be acceptable.
- ☐ The risk-benefit relationship of the research is not acceptable.
- ☐ If applicable, the additional information provided to subjects is acceptable.
- ☐ If applicable, the additional information provided to subjects is not acceptable.

Comments:



IRB Reviewer Signature

4/24/14

Date

INTEROFFICE MEMORANDUM

TO: CHAIR, IRB

FROM: THOMAS BUCHHEIT, MD



SUBJECT: SAE FOR PT. 127502 ON THE "REGIONAL ANESTHESIA AND VALPROATE SODIUM FOR THE PREVENTION OF CHRONIC POST-AMPUTATION PAIN" STUDY

DATE: 4/23/2014

Study Participant with ID # 127502, experienced an unexpected serious adverse event unrelated to the investigational agent on 04/12/2014; the study team was made aware on 04/18/2014. Attached is a copy of the Serious Unanticipated Problem/Serious Unanticipated Adverse Event Report Form with additional data for your review.

Durham VAMC Protocol Deviation Log

Instructions: Investigators may use this log to report protocol deviations that are not serious noncompliance and do not place one or more subjects at increased risk of harm. Submission of a completed log will satisfy the Continuing Review protocol deviation reporting requirement.

If a deviation is serious and unanticipated and places one or more subjects at increased risk of harm, report the deviation as a serious unanticipated problem on the Serious Unanticipated Problem/Unanticipated Serious Adverse Event report form within 5 business days of learning of the event. If deviation is apparent serious noncompliance, report within 5 business days of learning of the event.

SEP 25 '14 10:37

Protocol Deviation: Any departure, alteration, or procedural error in the IRB approved protocol and/or study procedure that occurs without prior IRB notification and approval. The cause of the deviation may be within the Investigator's control (e.g., change a protocol procedure or medication), or a deviation may not be in the control of the Investigator (e.g., a subject fails to show-up for a procedure defined in the protocol).

Serious Problem: A serious problem involves substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others; or substantively compromises the effectiveness of Durham VAMC's human research protection programs.

Unanticipated: An event or problem in VA research that is new or greater than previously known in terms of nature, severity, or frequency, given the procedures described in protocol-related documents and the characteristics of the study population.

Serious Noncompliance: Failure to adhere to the laws, regulations, or policies governing human research that might reasonably be regarded as involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research participants, research staff, or others; or substantively compromising the effectiveness of a VA facility's human research protection or human research oversight programs.

The following deviations did not meet criteria for a serious unanticipated problem or serious noncompliance and are being reported at Continuing Review (add additional rows as necessary):

Required Information			Optional Information	
Event Date	Subject ID (if applicable)	Description of Deviation	Reason for Deviation	Corrective Action
Deviation Log for Protocol # 01709 - Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain				
12/12/2013	127643	Blood Sample collected (13:30) prior to Study Drug Admin.(13:16) on the day of	Procedural Error	Study Team reviewed the process and the deviation was documented.

Durham VAMC Protocol Deviation Log

Required Information			Optional Information	
Event Date	Subject ID (if applicable)	Description of Deviation	Reason for Deviation	Corrective Action
		Surgery		
12/12/2013	127643	Patient missed 2 nd dose of study drug on day of surgery at 21:15.	Nurse states that the drug was not available	7 day supply of Investigational drug/placebo was placed in the Omnicell on the Day of Surgery. CRC spoke to Nurse Manager and Charge Nurse to remind nurses of drug location and to pass the information on to relief nurses.
12/16/2013	127643	Study Drug was stopped on Post Op Day 4 instead of Post Op Day 6 or up until the time of Discharge.	The patient complained of diarrhea and stomach pain for the past 2 days. PI was notified and the medication was stopped early.	The study drug administration is ceased if patient requests to discontinue and if PI determines to cease administration. The patient continued with the other components of the trial.
12/17/13	127644	Patient did not receive the night dose of study drug/placebo.	The drug was not administered and medical records logged as "not available"	Nurse Manager and Charge nurse were informed; nurses were reminded of the location of the study drug/placebo in the Omnicell and reminded to pass the information on to the nurse who relieves them during handover.
2/13/2014 to 2/14/2014	127646	Study Participant did not receive study drug or gave samples in Pre-op.	The patient's procedure occurred on a day when heavy snow and black ice prevented key study members (and staff) from being present to enroll the	The incident is logged as a deviation; In discussion with the Compliance Officer, the patient's participation in the study will end and a note will be made in CPRS at the end of

Durham VAMC Protocol Deviation Log

Required Information			Optional Information	
Event Date	Subject ID (if applicable)	Description of Deviation	Reason for Deviation	Corrective Action
			patient.	the study. The patient was made aware.
8/5/2014	127647	Missed month 1 questionnaires in May/June 2014.	Patient experienced an SAE during that time frame and indicated that he had not received the mailed questionnaires. No returned mail was received by the study team.	The patient completed the 'out of window' month 1 questionnaires at the month 3 visit in August 2014.
6/7/2014	127649	Study Drug stopped early	Clinician advise study team member that patient will be discharged early Saturday morning and end of study drug administration procedures commenced on 6/6/2014. On 6/7/2014 patient advised physician that he wasn't comfortable leaving the facility and discharge was postponed.	The study team communicates with the patient's care taking team on a daily basis to ensure that appropriate study procedures are conducted and will continue to do so. Patient's wishes will be respected and the deviation was documented.

Principal Investigator Signature: _____

Date: _____

ADVERSE EVENT TRACKING LOG

Study Title: DVAMC IRB Protocol # 01709 - Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

Study Coordinator: Dionne Apedjihoun

SEP 25 '14 10:37

Severity	Study Intervention Relationship	Action Taken Regarding Study Intervention	Outcome of AE	Expected
1 = Mild 2 = Moderate 3 = Severe	1 = Definitely related 2 = Possibly related 3 = Not related	1 = None 2 = Discontinued permanently 3 = Discontinued temporarily 4 = Reduced Dose 5 = Increased Dose 6 = Delayed Dose	1 = Resolved, No Sequel 2 = AE still present- no treatment 3 = AE still present-being treated 4 = Residual effects present-not treated 5 = Residual effects present- treated 6 = Death 7 = Unknown	1 = Yes 2 = No

	Subject ID	Start Date of Event	*Date Event Resolved	Description of Event	Severity	Study Intervention Relationship	Action Taken	Outcome of AE	Expected
1	127643	12/15/2013	12/18/2014	Diarrhea Patient had bowel movement on 12/15/13 and was given Maalox. C. difficile specimen sent for evaluation and	Moderate	Possibly related	Study drug/placebo was stopped.	Resolved, No Sequel	Yes – based on patient's antibiotic regimen and for MSSA from wound and other medications.
2	127643	12/16/2013	Ongoing	Left BKA irrigation and debridement with wound vac. placed	Mild	Not related	Natural Progression of the disease and does not require PI Intervention	AE still present-being treated Patient still has unhealed wound and continues to be evaluated.	Yes – Procedure is required due to the natural progression of the disease (cellulitis, infection) and is unrelated to the study drug
3	127643	12/17/2013	12/18/2014	Patient complained of chest pain when moving arms and with deep inspiration off and on over last couple days	Mild	Not related	Clinician notified and team continued to monitor patient.	Resolved, No Sequel	Yes – Patient has a diagnosis of COPD
4	127643	12/18/2013	12/20/2014	Nausea	Mild	Not related	Patient given Ondansetron, 8MG as needed for Nausea	Resolved, No Sequel	Yes – Based on Patient's drug regimen associated with his diagnosis.

ADVERSE EVENT TRACKING LOG

5	127643	12/18/2013	12/19/2014	Headache	Mild	Not related	Patient was given Tylenol	Resolved, No Sequel	No
6	127501	2/19/2014 (estimated)	3/5/2014	Hypoglycemia - Patient reported to pharmacist an episode of hypoglycemia 2 weeks prior.	Moderate	Not related	Patient reported that he is currently snacking at bedtime and occasionally between lunch and supper.	Resolved, No Sequel	Yes – Patient is Diabetic
7	127645	2/25/2014	3/6/2014	Otitis – While in the CLC, Patient complained of ear pain and on examination the left ear had wax " TM w/erythema, + fluid levels, yellow tint to fluid, pain w/movement "; the patient wears a hearing aid in this ear.	Mild	Not related	Patient was treated with pain medication and antibiotics (amox 250 q 8 x 7 days) while in the CLC	Resolved, No Sequel	No
8	127644	3/18/2014	3/18/2014	Fractured/decayed teeth to gingival margin.	Moderate	Not related	Patient had preplanned dental surgery for surgical extraction #'s 8 and 9 with alveoloplasty at the time of the month 3 visit.	Resolved, No Sequel	Yes- Patient discussed the need for oral surgery prior to study enrollment
9	127647	5/2/2014	5/2/2014	Left AKA (Above Knee Amputation) revision	Moderate	Not related	Procedure is required due to the natural progress of the disease - nonhealing infection of below-knee amputation.	Residual effects present-treated	Yes
10	127645	5/26/2014	6/27/2014	Abrasion in the gluteal fold region	Moderate	Not related	Patient treated with Moisture barrier cream and antifungal powder and patient was educated to dress wound	AE still present-being treated	No
11	127644	6/17/2014	8/25/2014	Superficial fungal infection (in skin fold) of Stump at the month 6 visit	Mild	Not related	Patient given antifungal cream	Resolved, No Sequel	No
12	127648	6/19/2014	6/20/2014	Fever – While in CLS, patient temp. went up to 102.8 °F.	Moderate	Not related	Evaluation indicated the presence of gram positive bacteria and patient was treated with "1 GM ceftriaxone ... Zosyn 3.375 IV q 6 hrs initiated 1st dose 11AM 6/19"	Resolved – fever resolved at 2AM	Yes – due to patient's diagnosis
13	127647	6/24/2014	6/25/2014	Fall – Patient fell in the bathroom of his home (sometime in the evening) resulting in skin tears on his left arm, a black left eye, and pain below his left shoulder. He reported that It hurts to breathe and cough.	Moderate	Not related	Patient was called by RN to assess injury, and he indicated that he was a little sore but refused to see a provider. He denied major injuries and	Resolved, No Sequel	Yes – due to age and comorbidity and that patient is an amputee.

ADVERSE EVENT TRACKING LOG

							indicated that his breathing had improved. He was encouraged to seek care if symptoms worsened.		
14	127502	8/28/2014		Diabetic Foot – Patient presented to Ed with lesion to left foot and reported a foul smell	Moderate	Not related	In the ED the wound was manually debrided and the flap of callused skin was removed. Wound dressed with silver nitrate pad and gauze pad. Patient was advised to seek medical attention otherwise f/u with podiatry as planned.	AE still present-being treated	Yes – Patient is Diabetic

Principal Investigator Signature: _____

Date: _____

Page 5 –Appendix G Certification
Human/Research and Development Continuation Review

PI: Thomas Buchheit, MD

MIRB/Promise #: 01709

Name of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

1. Circle the appropriate response:

a. When this study was initially approved, did it involve the use of biological, chemical, physical, or radiation hazards?	<input checked="" type="radio"/>	YES	NO
b. If the answer 1a is YES, are those hazards still in use, or has the study entered the data analysis phase such that hazards are no longer being used?	<input checked="" type="radio"/>	Hazards in use	Data analysis phase

If hazards are still in use, continue with questions 2 & 3. Otherwise, skip to the end and sign the form.


2. Circle the appropriate response for each of the following regarding the Appendix G approved at the initial review of this protocol, or at the last approved modification if applicable:

a. The safety program for this study remains as approved previously and described in the Appendix G.	<input checked="" type="radio"/>	TRUE	FALSE
b. If FALSE, append the revised Appendix G for review and approval.	<input checked="" type="radio"/>		See Attached
c. The chemical inventory remains the same.	<input checked="" type="radio"/>	N/A	TRUE FALSE
d. If FALSE, append revised Chemical Inventory.	<input checked="" type="radio"/>		See Attached
e. This study requires a Standard Operating Procedure for Human Blood, Tissues, and Cell Lines.	<input checked="" type="radio"/>	TRUE	FALSE
f. If TRUE, append an up-to-date copy of this SOP with bloodborne pathogen training and HepB vaccination data indicated for all personnel in this study.	<input checked="" type="radio"/>		See Attached
g. All other Standard Operating Procedures applicable to the study remain the same and require no further modification.	<input checked="" type="radio"/>	N/A	TRUE FALSE
h. If FALSE, append revised SOP.	<input checked="" type="radio"/>		See Attached

3. Circle the appropriate response for each of the following regarding safety training of research personnel:

a. Research personnel engaged in the collection of human samples or other samples containing biohazards that will be transported from the DVAMC to an offsite location have been appropriately trained. (See attached SOP) S:\Research Forms Jan 09\HUMAN FORMS Dec 08\Continuation Review Forms	<input checked="" type="radio"/>	N/A	TRUE FALSE
b. Research personnel that package and ship human samples or other samples containing biohazards have been trained. (See attached SOP) S:\Research Forms Jan 09\HUMAN FORMS Dec 08\Continuation Review Forms	<input checked="" type="radio"/>	N/A	TRUE FALSE
c. If TRUE for 3.b, append a current training certificate (note that certification is valid for two years.)	<input checked="" type="radio"/>		See Attached

Human/Research and Development Continuation Review

Principal Investigator Signature  Date 2/25/14

SOP: SRS-SOP 201	Research Using Human Blood, Tissue, or Cell Lines	Supersedes Document Dated: 9/21/2012
Version No: 05		
Effective Date: 03/15/2013		

Health Risks. Human blood, tissue, or cell lines may be contaminated with viruses including HIV, hepatitis B virus, and hepatitis C virus. All of these viruses have been transmitted to laboratory workers. All human materials will be presumed to contain infectious agents.

Training. All laboratory workers will receive annual training in **Bloodborne Pathogens and for all type(s) of safety needle devices used for injections, blood draws, or IV insertions**, when applicable. This training is accomplished as part of hospital-wide training programs at both Duke and the Durham VAMC. The PI will arrange for hands-on training for any safety needle device used by staff. The PI will also review this SOP with all laboratory workers during the initial orientation to the laboratory.

Health Precautions. All personnel who will work with human materials will be offered hepatitis B vaccination at the time of employment. There is no routine serological monitoring required.

Precautions and personal protective equipment. All work with human materials will be conducted at BSL2, as described in the CDC/NIH Handbook cited below. Key features of BSL2 for human materials include the following:

- Use of sharps and glass containers will be minimized.
- Use of a needle or sharp with a **safety device**.
- **Recapping of needles is discouraged. When recapping is required workers must use the one-handed technique.**
- Workers will wear **gowns and gloves**.
- **Workers will wear a face shield when not working in a biological safety cabinet (BSC) Class II.**
- All aerosol-generating manipulations will be conducted in a certified Class II BSC.

Response to an accidental exposure. Bloodborne pathogens can be transmitted via percutaneous exposures, mucous membranes, and contact with non-intact skin. Exposures must be promptly reported (LESS THAN ONE HOUR) to Occupational Health at the relevant institution (Duke or VA). When occupational health is closed, contact must be made via the Durham VAMC emergency room for VA Employees or via the Blood/Body Fluid Exposure Hotline for Duke Employees (684-8115). Responses to exposures may include laboratory testing of source patients or source materials, serologic monitoring of the exposed worker, and therapy to prevent infection with hepatitis B, hepatitis C, and/or HIV. Each institution has written occupational health policies in place regarding responses to these exposures.

Decontamination. Spills will be decontaminated using a 1:10 dilution of household bleach with a contact time of 10 minutes. **Dilution must be prepared just prior to decontamination.**

Disposal:

- **Sharps (needles, scalpels, pipettes, and broken contaminated glassware) must be disposed of in a puncture-resistant sharps container.**
- **Medical waste must be disposed of in a leak-proof biohazard bag.**
- **Environmental Management Services is responsible for picking up and disposing of all biohazard waste.**

References:

CDC/NIH. Biosafety in Microbiological and Biomedical Laboratories, 4th edition, 1999.

Durham VAMC Memorandum 558-99-5.154 (March 25, 1999). Exposure Control Plan for Bloodborne Pathogens


Durham VAMC Memorandum 5.118 (February 26, 1997). Management of Occupational Exposure to HIV.

29 CFR 1910.1030, Bloodborne Pathogens

Bloodborne Pathogen Standard Validation

Name (Only list Staff that will work with human blood, tissue, or cell lines)	Hep B Vaccine Has been Offered (Yes/No)	Current Date for Bloodborne Pathogen Training	Current Date of Competency for Use of a Needlestick Safety Devices , (if not applicable state N/A) List name and model of device
Dionne Apedjihoun	Yes	August 19, 2014	September 17, 2012 BD Vacutainer Safety Lok with Pre-Attached Holder, 23 G ¾ in. – 12 in. tubing REF 368653

I have read the above information and have validated in the table above the Hepatitis B vaccine offering, the required Bloodborne Pathogen, the competency on safety needle device(s) (when applicable), and SOP training for staff working on this protocol.


Principal Investigator


Date

Approved by: Sub-committee for Research Safety

Original Date: 03/01/2001

SOP: SRS-SOP 202 Version No: 05 Effective Date: 03/15/2013	Research Transporting and Shipping Biological Specimens	Supersedes Document Dated: 02/15/2013
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A. Internal Transport

- Laboratory specimens should be transported so that the integrity of the specimen and safety of the personnel and the transport system is maintained.
- Observe universal precautions and wear personal protective equipment (PPE) when handling and transporting specimens. Biohazard labels must be placed on all specimens.
- Do not transport specimens in a syringe or other container bearing a needle.
- Transport reusable sharps in a leak proof, puncture-resistant container.

B. Specimen Shipment

- Package specimens properly to protect them in transit as well as to protect the personnel handling them. Never mail a specimen in Petri plates. Never enclose dry ice in airtight (hermetically sealed) containers.
- Specimens shall be packed, packaged and labeled in full accordance with the Department of Transportation (DOT) and the International Air Transportation Association (IATA) requirements. All shipments originating from Durham VAMC Research & Development must comply with the Dangerous Goods Regulations (DGR).
- "Proper Shipment of Biological Materials" training is required by staff who package biological materials for land or air transport. Training must be renewed at least every two years.
- To receive training contact your Occupational Safety & Health Specialist, use CITI Program at www.citiprogram.org or the Duke module at <http://www.safety.duke.edu>.
- Packaging guidelines can be found at on the Duke OESO Safety website at <http://www.safety.duke.edu/LabSafety/Docs/Training%20Supplement%20Guide%20update.pdf> or as an attachment in the Research Laboratory Safety Manual.

References:

- The Centers for Disease Control and Prevention (CDC), the Department of Transportation (DOT), and the International Air Transport Association (IATA) dangerous goods guidelines

I have read the above information.


Principal Investigator (Signature)


Principal Investigator (Print)


Date

Listing of all staff that will package biological materials for land or air transport:

NAME	DATE AND SOURCE OF TRAINING
Dione Apedjain	10-21-2013 CITE : Packaging and Shipping of Ubers 6-2 Agents
Mary Kirkley	01-30-2012 Duke : Shipping Biological Materials OESO

Approved by: Sub-committee for Research Safety

Date: 03/15/2013

**Duke University and Duke Medicine
Occupational & Environmental Safety Office**

DIONNE APEDJIHOUN

Has Successfully Completed

Bloodborne Pathogens Training

on

August 19, 2014



**Duke University and Duke Medicine
Occupational & Environmental Safety Office**

MARY KIRKLEY

Has Successfully Completed

Shipping Biological Materials

on

January 30, 2012



COLLABORATIVE INSTITUTIONAL TRAINING INITIATIVE (CITI)
PACKAGING AND SHIPPING OF CLASS 6.2 AGENTS CURRICULUM COMPLETION REPORT
Printed on 10/21/2013

LEARNER	Dionne Brown Apedjihoun (ID: 656733) 229 Ranier Drive Raeferd NORTH CAROLINA 28376 United States
DEPARTMENT	Duke Anesthesiology
PHONE	7863904200
EMAIL	Dapedjihoun@gmail.com
INSTITUTION	Durham, NC-558
EXPIRATION DATE	10/21/2015

PACKAGING AND SHIPPING OF CLASS 6.2 AGENTS (FULFILLS IATA AND 49 CFR REGULATIONS)

COURSE/STAGE:	Basic Course/1
PASSED ON:	10/21/2013
REFERENCE ID:	11571955

REQUIRED MODULES

Packaging and Shipping of Class 6.2 Agents (Fulfills IATA and 49 CFR Regulations)

DATE COMPLETED

10/21/13

For this Completion Report to be valid, the learner listed above must be affiliated with a CITI Program participating institution or be a paid Independent Learner. Falsified information and unauthorized use of the CITI Program course site is unethical, and may be considered research misconduct by your institution.

Paul Braunschweiger Ph.D.
Professor, University of Miami
Director Office of Research Education
CITI Program Course Coordinator

DURHAM VAMC: RESEARCH STAFF LISTING

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain.

MIRB: 01709

Principal Investigator (signature required): 

Date: 9/25/14

The Staff Listing provides a list of all personnel who conduct any part of the research endeavor and must include the names of all individuals either involved in the conduct of the study or who make decision regarding study procedures. Staff Listings are required at initial review, annual continuing review, and anytime there is a change to Durham VAMC appointees. Changes in consultants or off-site VA personnel may be submitted at continuing review.

- Identify whether staff members are physically housed at the Durham VAMC or elsewhere.
- Any staff member that conducts any portion of research at the Durham VAMC must be covered by some type of VA appointment (i.e., VA-paid, WOC, or IPA) or be contracted to do so.
- Individuals who are not conducting the research but are associated with the study should be listed as a Consultant, regardless of VA appointment status (Note: Durham VAMC is not responsible for tracking research-required training for Consultants who do not have Durham VAMC appointments).
- If a researcher is employed at another VA institution, that individual should be listed on the Staff Listing, but their home VA is responsible for tracking educational requirements & the Scope of Practice.
- Use as many pages as necessary to list all staff.

Staff Member	Location	VA Appointment Type	Most Recent GCP/CITI Training Date for Durham VAMC appointees	Research Scope of Practice Note: Not applicable for Non-Durham VAMC appointees
Full Name: Thomas Buchheit Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Principal Investigator E-mail: thomas.buchheit@dm.duke.edu Phone: 286-0411 Ext. 5429	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	06/14/2014	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Hung-Lun (John) Hsia Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Co-Investigator E-mail: lun-hsia@dm.duke.edu Phone: 286-6938	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	08/12/2013	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Thomas Van de Ven Investigator: <input checked="" type="checkbox"/> Yes <input checked="" type="checkbox"/> No Study role: Collaborator E-mail: thomas.vandeven@dm.duke.edu Phone: 286-0411 Ext. 4926	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	03/14/2014	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Srinivas Pyati Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Co-Investigator E-mail: srinivas.pyati@dm.duke.edu Phone: 286-0411 Ext. 5384	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input checked="" type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	11/11/2012	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable

DURHAM VAMC: RESEARCH STAFF LISTING

Staff Member	Location	VA Appointment Type	Most Recent GCP/CITI Training Date for Durham VAMC appointees	Research Scope of Practice Note: Not applicable for Non-Durham VAMC appointees
Full Name: Juliann Hobbs Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Co-Investigator E-mail: juliann.hobbs@dm.duke.edu Phone: 286-0411 Ext. 4927	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	05/08/2013	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Karthik Raghunathan Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Co-Investigator E-mail: karthik.raghunathan@dm.duke.edu Phone: 286-6938	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	10/22/2012	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Cynthia Shortell Investigator: <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No Study role: Co-Investigator E-mail: cynthia.shortell@dm.duke.edu Phone: 286-0411	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input checked="" type="checkbox"/> Contract <input type="checkbox"/> Consultant	04/22/2013	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Sharon 'Becky' Perfect Investigator: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Study role: Clinical Trials Assistant E-mail: Sharon.Perfect@va.gov Phone: 286-0411 Ext. 7147	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input checked="" type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	08/14/2014	<input checked="" type="checkbox"/> On file <input checked="" type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Mary Kirkley Investigator: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Study role: Project Manager E-mail: mary.kirkley@dm.duke.edu Phone: 684-1170	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input checked="" type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	12/31/2013	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Dionne Apedjihoun Investigator: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Study role: Clinical Research Coordinator E-mail: dionne.apedjihoun@dm.duke.edu Phone: 286-0411 Ext. 7372	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input checked="" type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	06/10/2013	<input checked="" type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable

DURHAM VAMC: RESEARCH STAFF LISTING

Full Name: Meghan Jones Investigator: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No Study role: Clinical Trials Assistant E-mail: Meghan.Jones2@va.gov Phone: 286-0411 Ext. 2452	<input checked="" type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input checked="" type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	08/05/2013	<input checked="" type="checkbox"/> On file <input checked="" type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
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Staff Member	Location	VA Appointment Type	Most Recent GCP/CITI Training Date for Durham VAMC appointees	Research Scope of Practice <small>Note: Not applicable for Non-Durham VAMC appointees</small>
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant		<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable

DURHAM VAMC: RESEARCH STAFF LISTING

Full Name: Investigator: <input type="checkbox"/> Yes <input type="checkbox"/> No Study role: E-mail: Phone:	<input type="checkbox"/> Durham VAMC <input type="checkbox"/> Duke <input type="checkbox"/> Other VA facility <input type="checkbox"/> Other If VA/other, list: _____	<input type="checkbox"/> VA-paid <input type="checkbox"/> WOC <input type="checkbox"/> IPA <input type="checkbox"/> Contract <input type="checkbox"/> Consultant	<input type="checkbox"/> On file <input type="checkbox"/> Submitted with this Staff Listing <input type="checkbox"/> Not applicable
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**Research Informed Consent Form**

Version Date: 10/23/2013

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IRB Template: 2014-06-12

VA Form 10-1086

Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

Please read this form carefully. It tells you important information about a **voluntary** research study. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. It is important that you understand the information on this form. If you would like to check that this study is approved by the Durham VAMC's Institutional Review Board, please call the research office at (919) 286-6926 or (888) 878-6890, extension 6926.

WHY IS THIS RESEARCH BEING DONE?

The purpose of this research is to find out if a medication called Valproic Acid will prevent chronic nerve pain after amputation or limb injury surgery. Valproic acid (VPA) is already approved by the U.S. Food and Drug Administration (FDA) in the treatment of headaches and seizure disorders. The use of VPA in this study is investigational because VPA is not specifically approved by the FDA for use in preventing chronic pain after surgery. The word "investigational" means the study drug or device is still being tested in research studies and is not approved by the FDA for this particular use, although it may be approved for use in other cases.

You are being asked to participate in this research study because you are currently scheduled for amputation, stump revision surgery, or surgery on an arm or a leg with nerve damage at the Durham VA Medical Center. Before agreeing to participate in this research study, it is important that you read this consent form. It describes the purpose, procedures, benefits, known risks and discomforts of this study. You should take part in this study only if you want to do so. If this consent form contains any words or statements that you do not understand, please ask your study doctor or a member of the study staff to explain them. If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records. You are not required to take part in this study; your participation is entirely voluntary. However, in order to participate in this study, you must sign this form.

Approximately 420 patients in total will be enrolled, with plans to enroll 210 patients (50%) at the Durham VAMC. The remainder of the patients (approximately 210) will be enrolled at Walter Reed National Military Medical Center in Bethesda, MD. At the Durham VAMC, this study will take place in the preoperative clinics, surgical wards, intensive care unit and the Amputation Pain Clinic.

Subject Identification (last, first, middle) and Social Security Number:

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

VAMC: Durham

WHAT IS THE EXPERIMENTAL PART OF THIS RESEARCH STUDY?

This type of study is called a randomized, double-blinded, placebo-controlled clinical trial.

'Randomized' means that you will receive either a placebo (cherry syrup) or the active drug, valproic acid, which will taste like cherry syrup, during your enrollment in the study. This type of study is like flipping a coin. If you decide to participate in this study, you will have a 1-in-2 chance (50%) of receiving the cherry syrup instead of the active drug, valproic acid. 'Double-blinded' means that neither you nor any member of the research team will know if you received the cherry syrup or valproic acid. The VA Pharmacist will be the only person aware of the treatment you receive until the study is completed.

WHAT PROCEDURES, DRUGS, OR TREATMENTS ARE INVOLVED IN THIS RESEARCH STUDY?

If you agree to participate in this research study, and are enrolled, the staff will examine your medical record about relevant medical conditions/diseases to collect information such as clinic visits, lab and clinical test results. We will collect demographic information (name, address, telephone number, SSN, gender, ethnicity/race, age), surgical history (including prior amputation surgeries), and medical history (including medications, Body Mass Index, history of depression and PTSD) and pain scales. We will also collect the results of blood tests and events that occur during surgery and your hospital stay.

Before Surgery

1. After enrollment, a member of our research team will then ask you to:
 - a. Complete these questionnaires about your symptoms and any pain you may be experiencing: (Defense and Veterans Pain Rating Scale (DVPRS), Brief Pain Inventory (BPI), and the Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS). In addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions. If you have had a prior amputation, we will administer additional amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis). These will take approximately 15-20 minutes to complete.
 - b. Complete a brief clinical exam, and testing for level of sedation.
 - c. Give a blood sample (22ml which is approximately 1 ½ tablespoons) at the same time that an intravenous line is started for your routine anesthesia care. This blood sample will be used for research studies only.

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

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VAMC: Durham

2. You will then be given 250mg (approximately 1.5 teaspoons) of either the placebo or study drug. Both will taste like cherry syrup and will be given to you immediately before you are given anesthesia for your surgery and three times per day for the next 6 days from the time of the first dose, for a total of 7 days or until you are discharged from the hospital. This syrup (which may be either medication or placebo) is the experimental part of the study to see if the medication decreases the chances of chronic pain after surgery.
3. The remainder of your care (including activities, diet, medications, and surgical procedures and anesthesia type) will not be changed by enrollment in this study. All patients enrolled will receive a regional anesthesia catheter infusion for post-operative pain control, which is the current usual practice at the Durham VAMC.

Post-Operative Days 1 to 5

1. You will be asked to complete one very brief questionnaire (Defense and Veterans Pain Rating Scale (DVPRS) each day which will take approximately 5 minutes.
2. Your level of sedation will be assessed.
3. You will be given 250mg (approximately 1.5 teaspoons) of an oral placebo (cherry syrup) or oral valproic acid (flavored as cherry syrup) three times per day for 6 days following your surgery.
4. Total number of doses of the study drug to be given throughout 7 days will be 21 doses.

Post-Operative Day 6 – End of Study Drug

1. You will be asked to complete one very brief questionnaire (Defense and Veterans Pain Rating Scale (DVPRS), approximately 5 minutes.
2. Your level of sedation will be assessed.
3. You will receive the final dose of the study drug or placebo.
4. A blood sample of 34ml (approximately 2 tablespoons) will be collected. This blood will be used for research studies only.

One Month Following Surgery

Three brief pain questionnaires (DVPRS, BPI, and S-LANNS) will be sent to you by mail with a self-addressed, stamped envelope to be returned to the Clinical Research Coordinator for this study. These will be questionnaires that you have filled out during your hospital stay and will be familiar to you. This will take approximately 30 minutes. You will receive a follow-up phone call to verify that you have received the questionnaires and to document if there were any adverse events (unfavorable

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VAMC: Durham

medical occurrences) since your time of discharge from the hospital and to confirm that your month 3 appointment was scheduled.

Three Month Follow-up Visit to Durham VAMC Pain Clinic

1. You will be asked to complete several brief questionnaires (DVPRS, BPI, and S-LANNS) including Amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis) if an amputation was done; in addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions, approximately 30 minutes.
2. A final blood sample of 30ml (approximately 2 tablespoons) will be collected for experimental studies.
3. A brief physical exam will be performed.
4. If the month 3 follow-up visit is missed, you will be called to reschedule the appointment.
5. You will receive a check of \$50 for your participation in the study.

Six Month Follow-up Visit to Durham VAMC Pain Clinic

1. You will be asked to complete several brief questionnaires (DVPRS, BPI, and S-LANNS) including Amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis) if an amputation was done; in addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions, approximately 30 minutes.
2. A brief physical exam will be conducted.

WHAT GENETIC TESTING IS DONE IN THIS STUDY, AND WHAT IS THE RISK?

In this research, we are not only trying to find out if VPA may prevent chronic pain after surgery, but also how pain genes are turned on and off after injury. We will look for these changes in your blood, and determine if VPA is able to turn off some of these pain genes. Your blood samples will be barcoded, and only identifiable by the investigators through use of the code key that will be stored on a secure server behind the VA firewall. No personal health information (such as SSN or name) will be on samples that are analyzed outside of the Durham VAMC. DNA samples will remain barcoded so individuals working with samples or the database do not have access to personal information. No private genetic information will be provided to a 3rd party without your authorization.

We are not looking for existing genetic problems, and will not be able to tell you if you are at risk for other genetic diseases. This research is ONLY about pain and pain medicines, and we will not use your samples for other types of research. We will not provide your samples to any other researchers. Your samples will be stored at the Durham VAMC until they are sent to Duke or another outside lab for

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

analyses. When the tests are completed, the samples will be returned to the Durham VAMC. At the end of this study, your samples will be destroyed in accordance with current VA policy.

Informed Consent Regarding Genetic Testing: If you take part in this research you have the option to permit or deny the use of your DNA/RNA samples for genetic research by checking one of the following options:

I agree to genetic testing: ☐ Yes ☐ No

CAN I REFUSE TO BE IN THIS RESEARCH STUDY OR WITHDRAW AT A LATER TIME?

Absolutely. You do not have to join this or any other research study. If you do join and later change your mind, you may quit at any time. If you withdraw from the study, no new data about you will be collected for study purposes. If you refuse to join or if you withdraw from the study, there will be no penalty or loss of any benefits to which you are otherwise entitled. This will not affect your relationship with or treatment by the Veterans Health Administration (VHA) or your rights as a VHA patient. You will still receive all the medical care and benefits for which you are otherwise eligible.

If you decide to withdraw from the study during the experimental medication administration (within 7 days) you will be able to tell the clinical research coordinator during the daily study visits or call Dr Buchheit (919) 286-6938. If you wish to withdraw from the study after the completion of the study drug, we ask that you contact Dr. Thomas Buchheit in writing and let him know that you are withdrawing from the study. His mailing address is VAMC (112C) 508 Fulton Street, Durham, NC 27705. You should state that you no longer wish to take part in the study. If you withdraw this authorization, Dr. Buchheit and his research team will continue to use information about you that has been collected but no further information will be collected after you withdraw the authorization. This decision will not affect your care in any way at the Durham VAMC and your current medical regimen will continue without alteration.

WHAT OTHER OPTIONS DO I HAVE?

Taking part in this study is your choice. You have the option not to participate. The alternative to participating in this study is to have your surgery as planned by you and your surgeon and have pain medications issued to you in a routine manner. Your decision not to participate or to withdraw from

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**Participant Name:****Date:****Study Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

the study will not involve a penalty or loss of benefits to which you are entitled. It will not affect your access to health care at the DVAMC.

HOW LONG WILL I BE IN THIS RESEARCH STUDY?

Your participation in this study will last for up to 6 months. This period consists of up to 7 days for in-hospital care, questionnaires mailed to you at 1 month following your surgery and 2 follow-up visits to the Durham VA Pain Clinic at 3 months and 6 months following your surgery.

WHAT ARE THE RISKS AND DISCOMFORTS OF PARTICIPATING IN THIS RESEARCH STUDY?

The possible risks and discomforts from being in this research study include:

1. Risk from Blood Sample collection. Blood will be obtained in one of two ways: (1) it may be taken at the same time your intravenous (IV) catheter is started for your surgery; or (2) a needle will be inserted into a vein in your arm and small samples of blood will be taken. Collecting blood samples may cause pain and/or bruising at the site on your arm where your blood is taken and, rarely, fainting or infection. We estimate the risk of significant bruising is 10% (1 in 10).
2. Risk of Sedation (drowsiness). This risk will be minimized by starting all medications while you are admitted to the hospital. You will be closely monitored during the perioperative period, and will have ample opportunity to discontinue the study medication if you experience significant side effects. You will also have frequent monitoring for level of sedation during the study. We estimate the risk of significant sedation from VPA to be approximately 2% (1 in 50).
3. Risk in Pregnant Women. The study medication may increase risk of birth defects, including neural tube defects. This risk will be minimal as elective and semi-elective amputations are not performed during pregnancy. Additionally, a pregnancy test will be performed on all women of childbearing age who are to undergo surgery including amputation. If the pregnancy test is positive, the elective surgery is cancelled. If the surgery is performed under emergency circumstances, the patient will be excluded from the study. If you are pregnant and receive valproic acid there is a risk of congenital defects in approximately 3-4% (1 in 30) pregnancies.

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Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

4. Risk of Organ Toxicity. We have minimized risks of this study by using a drug (VPA) that has already been studied and approved by the Federal Drug Administration (FDA). This medication may cause some, all or none of these side-effects: sedation, confusion, and the remote possibility of organ and liver toxicity. You will be monitored closely and the blood samples collected will analyze your liver, blood count, and other organ function. We will further minimize risks of toxicity by administering the study drug for only 7 days and not using this drug for children or pregnant women where the risk is higher. The risk of significant toxicity in non-pregnant adults is rare (approximately 1 in 30,000 patients).
5. Risk of Interactions with other Medications. For your safety, you must tell the study doctor or nurse about all prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins and natural remedies that you are taking before you start the study. Certain medications interact with valproates. We will minimize risk of drug interactions by not enrolling you if you are on a medication with a strong interaction with VPA.
6. Risk of psychological distress. If something in this research makes you uncomfortable or upset, you may choose to stop taking part in the research at any time. If the investigator notes any distress or anxiety associated with the research, you will be referred to your primary care provider.
7. Social risks. Any breach of confidentiality arising from this study might potentially impact insurability, employability, reproduction plans, family relationships, immigration status, paternity suite, and/or social stigmatization. As mentioned above, we have reduced this risk to the bare minimum. VA healthcare benefits cannot be denied by the results of a genetic test.
8. Unknown risks. There may be unknown risks that we cannot predict. In addition, there may be future ramifications to you or your family members that are currently unclear or unknown. We have minimized the risks we know about, but we cannot protect against risks that may occur in the future.

Since this research may have bad effects on an unborn child and should not be done during pregnancy, we will give you a pregnancy test. If you are pregnant, we will withdraw you from the

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**Participant Name:****Date:****Study Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

study. You also agree to avoid becoming pregnant (use contraceptives, take precautions against becoming pregnant, etc.) during this study.

If you experience discomfort that you think may be related to the research, you can call the study team.

WILL I BENEFIT FROM TAKING PART IN THIS RESEARCH STUDY?

You may not personally be helped by taking part in this study, but your participation may lead to knowledge that will help others. It is known that VPA improves headache pain. What we do not know is whether or not it will prevent or reduce the nerve pain experienced after amputation or limb surgery. It is possible that use of the study drug, VPA, may make your pain better, but that cannot be promised or guaranteed. It is also possible that VPA could make your pain worse.

DOES PARTICIPATION IN THIS RESEARCH STUDY COST ANYTHING?

There will be no costs to you for any of the research treatment or research testing done as part of this research study. Some Veterans are required to pay co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

WILL I RECEIVE ANY COMPENSATION (MONEY OR OTHER) FOR TAKING PART IN THIS RESEARCH STUDY? HOW WILL I BE COMPENSATED?

Veterans will receive a one-time Check of \$50 after the 3 month follow-up visit, and will not receive additional monetary compensation as a result of any product of knowledge gained from the research. Your name, address, and Social Security Number only will be provided to Duke to issue this check.

ARE THERE REASONS THAT MY RESEARCH PARTICIPATION MAY END EARLY?

If there is evidence that administration of the study drug is causing harm to you, Dr Buchheit may terminate administration of the study drug without regard to consent in the interest of your safety. In this case you may be asked to continue in the study even though you did not complete the study drug administration.

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**Participant Name:****Date:****Study Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham**WHAT WILL HAPPEN IF I AM INJURED WHILE PARTICIPATING IN THE RESEARCH STUDY?**

The VA will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the Durham VAMC or arrangements may be made for contracted care at another facility. No promises have been given to you as the results and the risks of a research study are not always known in advance. Every reasonable safety measure will be taken to protect your well-being. You have not released this institution from liability for negligence. In case of research related injury resulting from this study, you should contact your study team. If you have questions about compensation and medical treatment for any study related injuries, you can call the medical administration service at this VA Medical Center at 919-286-6957.

WILL MY CLINICAL OR OTHER RESEARCH TEST RESULTS BE SHARED WITH ME?

We will let you and your physician know of any important discoveries made during this study which may affect you, your condition, or your willingness to participate in this study.

WILL THE RESULTS OF THIS RESEARCH STUDY BE SHARED WITH ME?

Subjects may receive a summary of the study results at the end of the study upon written request to the PI. No individualized information will be analyzed or released to study investigators or participants. Non-individual research results will only be released if: a) The findings are scientifically valid and confirmed, b) The findings have significant implications for the subject/patients health concerns, and c) A course of action to improve or treat these concerns is readily available and d) consultation and approval of the IRB is obtained.

DO ANY OF THE RESEARCHERS HAVE A FINANCIAL INTEREST RELATED TO THIS RESEARCH STUDY?

This study is being funded by the U.S. Department of Defense (DoD), Office of Congressionally Directed Medical Research Programs (CDMRP). Dr. Buchheit will not financially benefit from the study; however, the DoD will support the salaries of the research team.

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**Participant Name:****Date:****Study Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham**HOW WILL MY RESEARCH DATA BE PROTECTED AND SECURED?**

Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Patient research folders containing medical history and patient's Case Report Forms (CRF/questionnaires) will be in a locked file cabinet at the VAMC in Room C3011A. Only Dr. Buchheit and his research staff will have access to these folders. Electronic data will be stored in a restricted folder on the secure server also at the Durham VAMC. Data will only be accessed by members of the study team. PHI (Protected Health Information) sent to Duke will also be kept securely. Once payment is processed, your name and date only will be kept to track your payment and this is kept on a secure Duke University computer server.

Only de-identified data (all personal identifying information removed) will be entered into Research Electronic Data Capture (REDCap) – a secure, web-based application designed exclusively to support data capture for research studies. Data are housed on Duke Health Technology Solutions (DHTS) servers providing secured data. The Duke Translational Medical Institute (DTMI) instillation of REDCap has been validated and meets DTMI's understanding of HIPAA-compliance. Investigators will have secure password protected access to REDCap in order to enter and analyze data.

Only Dr. Buchheit and his research team will have access to this information. Blood samples will be labeled with a numerical study barcode. This code will not contain any information that can identify you. It will be linked to you via a computer file kept at the Durham VAMC on a secure computer server.

All barcoded blood samples will be sent to Duke University and/or Metabolon Inc., a diagnostics and services company in Raleigh, NC for further analysis as part of our research. The risk of your being identified by someone else is greater than if no linking file was kept at all, but is very small, and we cannot do the research without it. This level of labeling provides a high degree of confidentiality and provides you with significantly less risk than if your samples were labeled with your name. Some of these blood tests would have been done as part of your regular care. We will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record. Results of tests done solely for this research study and not as part of your regular care will also be included in your medical record.

There are VA rules (called records control requirements) about how long your research records are kept. Right now the rules say your research records cannot be destroyed. This may change in the

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**Research Informed Consent Form**

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IRB Template: 2014-06-12

VA Form 10-1086

Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

future; at that time we will follow the new VA rules. Your medical records will be maintained according to this medical center's requirements.

If results of this study are reported in medical journals or at meetings, you will not be identified by name, by recognizable photograph or by any other means without your specific consent. Your medical records will be maintained according to this medical center's requirements.

WILL ANYONE ELSE HAVE ACCESS TO MY RESEARCH DATA?

If results of this study are reported to others, you will not be identified by name, by recognizable photograph, or by any other means without your specific consent.

Your research records may be reviewed by Durham VA staff who are responsible for the safe conduct of this research. We may also disclose your information to federal agencies such as the Office for Human Research Protections (OHRP), the VA Office of the Inspector General (OIG), and the Office of Research Oversight (ORO). We will not share any information with these groups outside the VHA unless they agree to keep the information confidential and use it only for the purposes related to the study. Any information shared with these outside groups may no longer be protected under federal law. These groups may disclose your information to other groups. If the sponsor receives identified information, it is then the sponsor, and not the VA, who is responsible for the security of the information.

WHERE CAN I FIND OTHER INFORMATION ABOUT THIS RESEARCH STUDY?

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHO DO I CONTACT IF I HAVE QUESTIONS OR CONCERNS ABOUT THE RESEARCH STUDY?

If you have questions about the research or need to talk to the study team, you can contact the Dr. Thomas Buchheit at (919) 286-0411, extension 5429 during the day and at (919) 740-1099 after hours. You may also contact the study coordinator at (919) 286-0411 EXT 7372 during the day. If you have questions about the research or your rights as a research participant, would like to obtain

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**Research Informed Consent Form**

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Participant Name:**Date:****Study Title:** Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain**Principal Investigator:** Thomas Buchheit, MD**VAMC:** Durham

information, offer input, or have other concerns or complaints, you may contact the administrative officer of the research service at (919) 286-0411, extension 7632.

AFFIRMATION FROM PARTICIPANT

My rights as a research participant have been explained to me, and I voluntarily consent to participate in this study. I have received an explanation of what the study is about and how and why it is being done. I authorize the use and disclosure of my identifiable information as described in this form. I will receive a signed copy of this consent form. If I am a VA patient, a copy of this consent form will be placed in my medical record.

Participant's Signature_____
Date_____
Signature of Investigator or Person Obtaining Consent_____
Date**Unstamped forms are invalid**



Subject Name:

Date:

Title of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

VAMC: Durham

You are being asked to volunteer to take part in a research study at the Durham Veterans Affairs Medical Center (DVAMC). It is important that you read and understand the information in this form. If you would like to verify that this study is approved by the Durham VAMC's Institutional Review Board, please call the research office at (919) 286-6926.

PURPOSE

The purpose of this research is to find out if a medication called Valproic Acid will prevent chronic nerve pain after amputation or limb injury surgery. Valproic acid (VPA) is already approved by the U.S. Food and Drug Administration (FDA) in the treatment of headaches and seizure disorders. The use of VPA in this study is investigational because VPA is not specifically approved by the FDA for use in preventing chronic pain after surgery. The word "investigational" means the study drug or device is still being tested in research studies and is not approved by the FDA for this particular use, although it may be approved for use in other cases.

Approximately 420 patients in total will be enrolled, with plans to enroll 210 patients (50%) at the Durham VAMC. The remainder of the patients (approximately 210) will be enrolled at Walter Reed National Military Medical Center in Bethesda, MD. At the Durham VAMC, this study will take place in the preoperative clinics, surgical wards, intensive care unit and the Amputation Pain Clinic.

This study is being funded by the U.S. Department of Defense (DoD), Office of Congressionally Directed Medical Research Programs (CDMRP). Dr. Buchheit will not financially benefit from the study; however, the DoD will support the salaries of the research team.

You are being asked to participate in this clinical trial because you are currently scheduled for amputation, stump revision surgery, or surgery on an arm or a leg with nerve damage at the Durham VA Medical Center. Before agreeing to participate in this research study, it is important that you read this consent form. It describes the purpose, procedures, benefits, known risks and discomforts of this study. You should take part in this study only if you want to do so. If this consent form contains any words or statements that you do not understand, please ask your study doctor or a member of the study staff to explain them. If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

This type of study is called a randomized, double-blinded, placebo-controlled clinical trial. 'Randomized' means that you will receive either a placebo (cherry syrup) or the active drug, valproic acid, which will taste like cherry syrup, during your enrollment in the study. This type of study is like flipping a coin. You will have a 1-in-2 chance (50%) of receiving the cherry syrup instead of the active drug, valproic acid. 'Double-blinded' means that neither you nor any member of the research team will know if you received the cherry syrup or valproic acid. The VA Pharmacist will be the only person aware of the treatment you receive until the study is completed.

SUBJECT IDENTIFICATION (I.D. plate of give name - last, first, middle) and SOCIAL SECURITY NUMBER

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Subject Name:	Date:
Title of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain	
Principal Investigator: Thomas Buchheit, MD	VAMC: Durham

PROCEDURES

If you consent to be in this study and are enrolled, the staff will examine your medical record about relevant medical conditions/diseases to collect information such as clinic visits, lab and clinical test results. We will collect demographic information (name, address, telephone number, SSN, gender, ethnicity/race, age), surgical history (including prior amputation surgeries), and medical history (including medications, Body Mass Index, history of depression and PTSD) and pain scales. We will also collect the results of blood tests and events that occur during surgery and your hospital stay.

Before Surgery

1. After enrollment, a member of our research team will then ask you to:
 - a. Complete these questionnaires about your symptoms and any pain you may be experiencing: (Defense and Veterans Pain Rating Scale (DVPRS), Brief Pain Inventory (BPI), and the Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS). In addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions. If you have had a prior amputation, we will administer additional amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis). These will take approximately 15-20 minutes to complete.
 - b. Complete a brief clinical exam, and testing for level of sedation.
 - c. Give a blood sample (22ml which is approximately 1 ½ tablespoons) at the same time that an intravenous line is started for your routine anesthesia care. This blood sample will be used for research studies only.
2. You will then be given 250mg (approximately 1.5 teaspoons) of either the placebo or study drug. Both will taste like cherry syrup and will be given to you immediately before you are given anesthesia for your surgery and three times per day for the next 6 days from the time of the first dose, for a total of 7 days or until you are discharged from the hospital. This syrup (which may be either medication or placebo) is the experimental part of the study to see if the medication decreases the chances of chronic pain after surgery.
3. The remainder of your care (including activities, diet, medications, and surgical procedures and anesthesia type) will not be changed by enrollment in this study. All patients enrolled will receive a regional anesthesia catheter infusion for post-operative pain control, which is the current usual practice at the Durham VAMC.

Post-Operative Days 1 to 5

1. You will be asked to complete one very brief questionnaire (Defense and Veterans Pain Rating Scale (DVPRS) each day which will take approximately 5 minutes.

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2. Your level of sedation will be assessed.
3. You will be given 250mg (approximately 1.5 teaspoons) of an oral placebo (cherry syrup) or oral valproic acid (flavored as cherry syrup) three times per day for 6 days following your surgery.
4. Total number of doses of the study drug to be given throughout 7 days will be 21 doses.

Post-Operative Day 6 – End of Study Drug

1. You will be asked to complete one very brief questionnaire (Defense and Veterans Pain Rating Scale (DVPRS), approximately 5 minutes.
2. Your level of sedation will be assessed.
3. You will receive the final dose of the study drug or placebo.
4. A blood sample of 34ml (approximately 2 tablespoons) will be collected. This blood will be used for research studies only.

One Month Following Surgery

Three brief pain questionnaires (DVPRS, BPI, and S-LANNS) will be sent to you by mail with a self-addressed, stamped envelope to be returned to the Clinical Research Coordinator for this study. These will be questionnaires that you have filled out during your hospital stay and will be familiar to you. This will take approximately 30 minutes. You will receive a follow-up phone call to verify that you have received the questionnaires and to document if there were any adverse events (unfavorable medical occurrences) since your time of discharge from the hospital and to confirm that your month 3 appointment was scheduled.

Three Month Follow-up Visit to Durham VAMC Pain Clinic

1. You will be asked to complete several brief questionnaires (DVPRS, BPI, and S-LANNS) including Amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis) if an amputation was done; in addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions, approximately 30 minutes.
2. A final blood sample of 30ml (approximately 2 tablespoons) will be collected for experimental studies.
3. A brief physical exam will be performed.
4. If the month 3 follow-up visit is missed, you will be called to reschedule the appointment.
5. You will receive a check of \$50 for your participation in the study.

Six Month Follow-up Visit to Durham VAMC Pain Clinic

1. You will be asked to complete several brief questionnaires (DVPRS, BPI, and S-LANNS) including Amputation questionnaires (Phantom Limb Pain, Residual Limb pain and Prosthesis) if an amputation was done; in addition you will be evaluated with the Complex Regional Pain Syndrome (CRPS) and Neuroma Questions, approximately 30 minutes.
2. A brief physical exam will be conducted.

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Principal Investigator: Thomas Buchheit, MD

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Your participation in this study will last for up to 6 months. This period consists of up to 7 days for in-hospital care, questionnaires mailed to you at 1 month following your surgery and 2 follow-up visits to the Durham VA Pain Clinic at 3 months and 6 months following your surgery.

COLLECTION, STORAGE, USE OF DNA AND OTHER GENETIC RELATED SAMPLES

In this research, we are not only trying to find out if VPA may prevent chronic pain after surgery, but also how pain genes are turned on and off after injury. We will look for these changes in your blood, and determine if VPA is able to turn off some of these pain genes. Your blood samples will be barcoded, and only identifiable by the investigators through use of the code key that will be stored on a secure server behind the VA firewall. No personal health information (such as SSN or name) will be on samples that are analyzed outside of the Durham VAMC. DNA samples will remain barcoded so individuals working with samples or the database do not have access to personal information. No private genetic information will be provided to a 3rd party without your authorization.

We are not looking for existing genetic problems, and will not be able to tell you if you are at risk for other genetic diseases. This research is ONLY about pain and pain medicines, and we will not use your samples for other types of research. We will not provide your samples to any other researchers. Your samples will be stored at the Durham VAMC until they are sent to Duke or another outside lab for analyses. When the tests are completed, the samples will be returned to the Durham VAMC. At the end of this study, your samples will be destroyed in accordance with current VA policy.

Informed Consent Regarding Genetic Testing: If you take part in this research you have the option to permit or deny the use of your DNA/RNA samples for genetic research by initialing one of the following options:

_____ "Yes, I agree to allow my DNA/RNA blood sample to be used for genetic research."

_____ "No, I do not allow my DNA/RNA blood sample to be used for genetic research."

DISCOMFORTS AND RISKS

The possible risks and discomforts from being in this research study include:

1. Risk from Blood Sample collection. Blood will be obtained in one of two ways: (1) it may be taken at the same time your intravenous (IV) catheter is started for your surgery; or (2) a needle will be inserted into a

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vein in your arm and small samples of blood will be taken. Collecting blood samples may cause pain and/or bruising at the site on your arm where your blood is taken and, rarely, fainting or infection. We estimate the risk of significant bruising is 10% (1 in 10).

2. Risk of Sedation (drowsiness). This risk will be minimized by starting all medications while you are admitted to the hospital. You will be closely monitored during the perioperative period, and will have ample opportunity to discontinue the study medication if you experience significant side effects. You will also have frequent monitoring for level of sedation during the study. We estimate the risk of significant sedation from VPA to be approximately 2% (1 in 50).
3. Risk in Pregnant Women. The study medication may increase risk of birth defects, including neural tube defects. This risk will be minimal as elective and semi-elective amputations are not performed during pregnancy. Additionally, a pregnancy test will be performed on all women of childbearing age who are to undergo surgery including amputation. If the pregnancy test is positive, the elective surgery is cancelled. If the surgery is performed under emergency circumstances, the patient will be excluded from the study. If you are pregnant and receive valproic acid there is a risk of congenital defects in approximately 3-4% (1 in 30) pregnancies.
4. Risk of Organ Toxicity. We have minimized risks of this study by using a drug (VPA) that has already been studied and approved by the Federal Drug Administration (FDA). This medication may cause some, all or none of these side-effects: sedation, confusion, and the remote possibility of organ and liver toxicity. You will be monitored closely and the blood samples collected will analyze your liver, blood count, and other organ function. We will further minimize risks of toxicity by administering the study drug for only 7 days and not using this drug for children or pregnant women where the risk is higher. The risk of significant toxicity in non-pregnant adults is rare (approximately 1 in 30,000 patients).
5. Risk of Interactions with other Medications. For your safety, you must tell the study doctor or nurse about all prescription drugs, herbal products, over-the-counter (OTC) drugs, vitamins and natural remedies that you are taking before you start the study. Certain medications interact with valproates. We will minimize risk of drug interactions by not enrolling you if you are on a medication with a strong interaction with VPA.
6. Risk of psychological distress. If something in this research makes you uncomfortable or upset, you may choose to stop taking part in the research at any time. If the investigator notes any distress or anxiety associated with the research, you will be referred to your primary care provider.
7. Social risks. Any breach of confidentiality arising from this study might potentially impact insurability.

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employability, reproduction plans, family relationships, immigration status, paternity suite, and/or social stigmatization. As mentioned above, we have reduced this risk to the bare minimum. VA healthcare benefits cannot be denied by the results of a genetic test.

8. Unknown risks. There may be unknown risks that we cannot predict. In addition, there may be future ramifications to you or your family members that are currently unclear or unknown. We have minimized the risks we know about, but we cannot protect against risks that may occur in the future.

BENEFITS

You may not personally be helped by taking part in this study, but your participation may lead to knowledge that will help others. It is known that VPA improves headache pain. What we do not know is whether or not it will prevent or reduce the nerve pain experienced after amputation or limb surgery. It is possible that use of the study drug, VPA, may be better, but that cannot be promised or guaranteed. It is also possible that VPA could make your pain worse."

OTHER TREATMENT AVAILABLE

The alternative to participating in this study is to have your surgery as planned by you and your surgeon and have pain medications issued to you in a routine manner. Your decision not to participate or to withdraw from the study will not involve a penalty or loss of benefits to which you are entitled. It will not affect your access to health care at the DVAMC.

RESEARCH RESULTS

1. We will let you and your physician know of any important discoveries made during this study that may affect you, your condition, or your willingness to participate in this study.
2. Study records that identify you will be kept confidential as required by law. Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. The original paper files will be kept in a locked file cabinet in the Anesthesiology Service research office, Room C3011A at the Durham VAMC. Electronic data will be stored in a restricted folder on the secure server also at the Durham VAMC. Data will only be accessed by members of the study team. Paper information will be shredded in accordance with the VA requirements for destruction of sensitive information and information in electronic format will be deleted or purged from data files in accordance with VA records control requirements indefinitely.
3. If results of this study are reported in medical journals or at meetings, you will not be identified by name, by

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recognizable photograph or by any other means without your specific consent. Your medical records will be maintained according to this medical center's requirements.

4. As part of this study, we may disclose your information and medical and/or research records to the Office for Human Research Protections (OHRP), representatives of the USAMRMC (DOD), the VA Office of the Inspector General (OIG), other government agencies, the Office of Research Oversight (ORO), the Durham VAMC Institutional Review Board (IRB), and/or the Food and Drug Administration (FDA). We will not share any information with these groups outside the VHA unless they agree to keep the information confidential and use it only for the purposes related to the study. Any information shared with these outside groups may no longer be protected under federal law, and, furthermore, these groups may disclose your information to other groups. If the sponsor receives identified information, the sponsor and not the VA, is then responsible for the security of the information.
5. Subjects may receive a summary of the study results at the end of the study upon written request to the PI. No individualized information will be analyzed or released to study investigators or participants. Non-individual research results will only be released if: a) The findings are scientifically valid and confirmed, b) The findings have significant implications for the subject/patients health concerns, and c) A course of action to improve or treat these concerns is readily available and d) consultation and approval of the IRB is obtained.

COMPENSATION

Veterans will receive a one-time Check of \$50 after the 3 month follow-up visit, and will not receive additional monetary compensation as a result of any product of knowledge gained from the research. Your name, address, and Social Security Number only) will be provided to Duke to issue this check.

SPECIAL INFORMATION

1. You are not required to take part in this study: your participation is entirely voluntary. However, in order to participate in this study, you must sign this form.
2. You can refuse to participate now or you can withdraw from the study at any time after giving your consent. This will not interfere with your payment, enrollment, eligibility for benefits, or your regular medical treatment, if you are a patient.
3. You may decide to not enroll in this study or you may decide to not continue in the study later if you change your mind. If you decide to withdraw from the study during the experimental medication administration (within

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7 days) you will be able to tell the clinical research coordinator during the daily study visits or call Dr Buchheit (919) 286-6938. If you wish to withdraw from the study after the completion of the study drug, we ask that you contact Dr. Thomas Buchheit in writing and let him know that you are withdrawing from the study. His mailing address is VAMC (112C) 508 Fulton Street, Durham, NC 27705. You should state that you no longer wish to take part in the study. If you withdraw this authorization, Dr. Buchheit and his research team will continue to use information about you that has been collected but no further information will be collected after you withdraw the authorization. This decision will not affect your care in any way at the Durham VAMC and your current medical regimen will continue without alteration.

4. There will be no costs to you for any of the treatment or testing done as part of this research study. Some veterans are required to pay co-payments for medical care and services provided by VA. These co-payments requirements will continue to apply to medical care and services provided by VA that are not part of this study.
5. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Patient Records and Sample Labeling

In this research, patient identifiers will be stored at the VAMC with restricted access on the secure Durham VAMC computer server. Patient research folders containing medical history and patient's Case Report Forms (CRF/questionnaires) will be in a locked file cabinet at the VAMC in Room C3011A. Only Dr. Buchheit and his research staff will have access to these folders. PHI (Protected Health Information) sent to Duke will also be kept securely. Once payment is processed, your name and date only will be kept to track your payment and this is kept on a secure Duke University computer server.

Only de-identified data will be entered using REDCap.

Only de-identified data will be entered into Research Electronic Data Capture (REDCap) – a secure, web-based application designed exclusively to support data capture for research studies. Data are housed on Duke Health Technology Solutions (DHTS) servers providing secured data. The Duke Translational Medical Institute (DTMI) instillation of REDCap has been validated and meets DTMI's understanding of HIPAA-compliance. Investigators will have secure password protected access to REDCap in order to enter and analyze data.

Only Dr. Buchheit and his research team will have access to this information. Blood samples will be labeled with a numerical study barcode. This code will not contain any information that can identify you. It will be linked to you via a computer file kept at the Durham VAMC on a secure computer server.

All barcoded blood samples will be sent to Duke University and/or Metabolon Inc., a diagnostics and services

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company in Raleigh, NC for further analysis as part of our research. The risk of your being identified by someone else is greater than if no linking file was kept at all, but is very small, and we cannot do the research without it. This level of labeling provides a high degree of confidentiality and provides you with significantly less risk than if your samples were labeled with your name. Some of these blood tests would have been done as part of your regular care. We will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record. Results of tests done solely for this research study and not as part of your regular care will also be included in your medical record.

There will be no costs to you for any of the treatment or testing done as part of this research study. Some veterans are required to make co-payments for medical care and services provided by VA. These co-payment requirements will continue to apply to medical care and services provided by VA that are not part of this study.

If there is evidence that administration of the study drug is causing harm to you, Dr Buchheit may terminate administration of the study drug without regard to consent in the interest of your safety. In this case you may be asked to continue in the study even though you did not complete the study drug administration.

Eligibility for medical care is based upon the usual VA eligibility policy and is not guaranteed by participation in a research study.

The VA will provide necessary medical treatment should you be injured by being in this study. You will be treated for the injury at no cost to you. This care may be provided by the Durham VAMC or arrangements may be made

for contracted care at another facility. No promises have been given to you as the results and the risks of a research study are not always known in advance. Every reasonable safety measure will be taken to protect your well-being. You have not released this institution from liability for negligence. In case of research related injury resulting from this study, you should contact the Dr. Thomas Buchheit at (919) 286-0411, extension 5429 during the day and at (919) 740-1099 after hours. Further information about compensation and medical treatment may be obtained from the medical administration service at (919) 286-6957 at this VA medical center.

If you have questions about the research or your rights as a research subject, would like to obtain information, offer input, or have other concerns or complaints, you may contact the administrative officer of the research service at (919) 286-0411 ext. 7632.

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Principal Investigator: Thomas Buchheit, MD

VAMC: Durham

AFFIRMATION FROM SUBJECT

RESEARCH SUBJECTS RIGHTS: I have read or have had read to me all of the above. Dr. Buchheit or his staff has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

I have been told that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of benefits to which I am entitled. I may withdraw from this study at any time without penalty of loss of VA or other benefits to which I am entitled. To withdraw from the study, I should write to Dr. Buchheit, at Durham VAMC, 508 Fulton Street, 112C, Durham, NC 27705. I understand that if I withdraw from the study, no new data about me will be collected for study purposes other than data needed to keep track of my withdrawal. However, the research team may continue to use data about me collected prior to the date of withdrawal.

The results of this study may be published, but my records will not be revealed unless required by law. In case there are questions, concerns, or complaints regarding this research study, I have been told I can call Dr. Buchheit at (919) 286-0411, ext. 5284 during the day and at (919) 970-1858 after hours. If any medical problems occur in connection with this study the VA will provide care.

My rights as a research subject have been explained to me, and I voluntarily consent to participate in this study. I have received an explanation of what the study is about and how and why it is being done. I authorize the use and disclosure of my identifiable information as described in this form. I will receive a signed copy of this consent form. If I am a VA patient, a copy of this consent form will be placed in my medical record.

Subject's Signature_____
Date_____
Signature of Investigator or Person Obtaining Consent_____
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Department of Veterans Affairs

HIPAA Authorization for Release of Protected Health Information for Research Purposes

PI Version: October 23, 2013

VAMC: Durham

Template: 2014-06-12

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

HIPAA (Health Insurance Portability & Accountability Act) is a federal privacy law that protects the confidentiality of health information collected about you. The following explains how health information collected about you will be used by the investigators and who they may share your health information with as part of this research.

What is the purpose of this research study?

You have been asked to participate in a research study under the direction of Dr. Thomas Buchheit, Principal Investigator, and his research team. The purpose of this study is to test the effectiveness of an FDA approved medication, called Valproic Acid (VPA), to see if it can be used to prevent chronic nerve and post-amputation pain.

How will my health information be used in this research study?

Information obtained from this study will be used in the following ways:

<input checked="" type="checkbox"/> Learn more about the disease/condition being studied
<input type="checkbox"/> Learn more about the costs of treating the disease/condition being studied
<input checked="" type="checkbox"/> Improve health care for persons with the disease/condition being studied
<input checked="" type="checkbox"/> Analyze research results
<input checked="" type="checkbox"/> Facilitate treatment, payment, and/or operations related to the study
<input checked="" type="checkbox"/> Monitor for adverse events/side effects
<input checked="" type="checkbox"/> Determine the safety and effectiveness of the treatment(s)
<input type="checkbox"/> Perform quality assessments related to (Veterans Health Administration (VHA) research
<input type="checkbox"/> Other, describe:

What Personal Health Information will be used or shared?

The following health information, linked to you by the following identifiers, will be used in this research study:

Identifier(s)	Source(s) of Health Information
<input checked="" type="checkbox"/> Names	<input checked="" type="checkbox"/> Medical history & physical exam information Describe: BMI (Body Mass Index), Significant Medical and Surgical History, Narcotic Medication. History of PTSD and Depression, Pain Scales)
<input checked="" type="checkbox"/> All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code Describe: Address will be used for mailing checks for study participation	<input type="checkbox"/> Photographs, videotapes, audiotapes, or digital or other images Describe:



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Participant Name:

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Principal Investigator: Thomas Buchheit, MD

Identifier(s)	Source(s) of Health Information
<input checked="" type="checkbox"/> All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89 Describe: dates to be collected are date of surgery, birth, discharge, 3 and 6 month follow-up appointments	<input checked="" type="checkbox"/> Biologic specimens (e.g., blood, tissue, urine, saliva) Describe: Blood
<input checked="" type="checkbox"/> Telephone numbers	<input checked="" type="checkbox"/> Progress notes
<input type="checkbox"/> Fax numbers	<input checked="" type="checkbox"/> Diagnostic / Laboratory test results
<input type="checkbox"/> Electronic mail addresses	<input checked="" type="checkbox"/> Operative reports
<input checked="" type="checkbox"/> Social Security Numbers	<input checked="" type="checkbox"/> Imaging (x-ray, CT, MRI, etc.)
<input checked="" type="checkbox"/> Medical record numbers	<input checked="" type="checkbox"/> Discharge summaries
<input type="checkbox"/> Health plan beneficiary numbers	<input checked="" type="checkbox"/> Survey / Questionnaire responses
<input type="checkbox"/> Account numbers	<input type="checkbox"/> Billing records
<input type="checkbox"/> Certificate and/or license numbers	<input type="checkbox"/> HIV testing or infection records
<input type="checkbox"/> Vehicle identifiers and serial numbers, including license plate numbers	<input type="checkbox"/> Sickle cell anemia information
<input type="checkbox"/> Device identifiers and serial numbers	<input type="checkbox"/> Alcoholism or alcohol use information
<input type="checkbox"/> Web Universal Resource Locators (URLs)	<input type="checkbox"/> Drug abuse information
<input type="checkbox"/> Internet Protocol (IP) address numbers	<input checked="" type="checkbox"/> Mental health (not psychotherapy) notes
<input type="checkbox"/> Biometric identifiers, including finger & voice prints	<input type="checkbox"/> Psychological test results
<input type="checkbox"/> Full-face photographic images and any comparable images	<input type="checkbox"/> Genetic testing
<input type="checkbox"/> Any other unique identifying number, characteristic, or study code Describe:	<input checked="" type="checkbox"/> Other, describe: Tobacco use, Gender, Ethnicity/Race

Who may use or share my Health Information?

By signing this authorization, you allow the following individuals and entities to obtain, use, and share your health information for this research study:

- The Principal Investigator Dr. Thomas Buchheit and members of his research team.
- Departments within the VA which are responsible for the oversight, administration, or conduct of research.

Who may receive and use my Health Information?



Department of Veterans Affairs

HIPAA Authorization for Release of Protected Health Information for Research Purposes

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VAMC: Durham

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

As part of the study, we may disclose your information and medical and/or research records to:

- The Office for Human Research Protections (OHRP), and representatives of the USAMRMC (DOD).
- Compliance and safety monitors who conduct on-site or off-site data reviews.
- The Durham VAMC's Institutional Review Board and Research Compliance Officers.
- The Office for Human Research Protections (OHRP).
- Departments within the VA which are responsible for the oversight, administration, or conduct of research.
- Other government agencies.
- For compensation for participation in the study, Duke University will collect your name, address and social security number to process payment.

The Durham VAMC complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all other applicable laws that protect your privacy. We will protect your information according to these laws. We will not share any information with these groups outside the VHA unless they agree to keep the information confidential and use it only for the purposes related to the study. Despite these protections, there is a possibility that the recipient(s) of your information could use or disclose your information in such a way that it will no longer be protected. Our Notice of Privacy Practices (a separate document) provides more information on how we protect your information. You may find the Notice at http://www1.va.gov/vhapublications/ViewPublication.asp?pub_ID=1089.

If the sponsor receives identified information, it is then the sponsor, and not the VA, who is responsible for the security of the information

Do I have to sign this form?

No. Signing this form is voluntary. The VA does not condition treatment, payment, enrollment or eligibility for benefits based on signing this form. If you decide not to sign this form, you will not be able to take part in this study.

If I sign now, can I decide later not to continue in the study?

Yes. You are free to take back your permission and stop being in the study. The investigators will not collect any more information about you after you take back your permission, but they can continue to use your information that was collected before you took back your permission.

Your request to take back your permission must be done in writing. Either give or send your written request to the investigator: Dr. Thomas Buchheit, DVAMC (112C), 508 Fulton Street, Durham, NC 27705.



Department of Veterans Affairs

**HIPAA Authorization for Release of Protected Health
Information for Research Purposes**

PI Version: October 23, 2013

VAMC: Durham

Template: 2014-06-12

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Participant Name:

Date:

Study Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Principal Investigator: Thomas Buchheit, MD

Does my permission for the use of my Personal Health Information expire?


Unless you revoke (take back) your permission, your authorization to allow us to use and/or disclose your information will:

- ☒ Expire at the end of this research study
☐ Not expire because the data and/or specimens will reside in a research repository
☐ Expire on the following date or event:

Signature of Participant:

Full SSN:

Date:

 Department of Veterans Affairs		HIPAA Authorization for Release of Protected Health Information for Research Purposes	
Title of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain		Version Date: 10/23/2013	
Principal Investigator: Thomas Buchheit, MD		VAMC: Durham	

You have been asked to participate in a research study under the direction of Dr. Thomas Buchheit, Principal Investigator, and his research team. The purpose of this study is to test the effectiveness of an FDA approved medication, called Valproic Acid (VPA), to see if it can be used to prevent chronic nerve and post-amputation pain.

By signing this document, you will authorize the Veterans Health Administration (VHA) to provide Dr. Buchheit and his research team the authority to use and disclose the following Personal Health Information (PHI) about you:

- Demographics (name, address, telephone number, SSN, gender, ethnicity/race, age, Body Mass Index, dates to be collected are date of surgery, birth, discharge, 3 and 6 month follow-up appointments).
- Significant medical and surgical history.
- Narcotic Medication (Total daily morphine equivalent dose)
- History of PTSD
- History of depression
- Pain scales

All of this information about you will be kept private and secured in the Anesthesiology Research office. Your private health information will be respected and research will be conducted such that you will not be personally identifiable.

During the course of the study, you will be asked to complete a variety of questionnaires (5 in total), some will be repeated at different time points. The time to complete each questionnaire is 5 to 10 minutes.

You do not have to sign this Authorization. If you decide not to sign the Authorization:


- It will not affect your regular medical care and rights as a VHA patient.
- You will not be allowed to participate in this research study.

At present, records for any research that involves the VA must be retained indefinitely per VA federal regulatory requirements and is subject to change. This authorization will expire at the end of the research study. At the conclusion of the study, any remaining blood samples will be destroyed in accordance with VHA requirements.

You can withdraw this authorization at any time. To withdraw your authorization, you can write to Dr.

IMPRINT PATIENT DATA CARD

APPROVED
12/12/13

 Department of Veterans Affairs		HIPAA Authorization for Release of Protected Health Information for Research Purposes
Title of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain		Version Date: 10/23/2013
Principal Investigator: Thomas Buchheit, MD		VAMC: Durham

Buchheit, Durham VAMC, Anesthesiology Service, Room D5006, 508 Fulton St, Durham, 27705 or you can ask a member of the research team to give you a form to withdraw the authorization. If you withdraw this authorization, you will not be able to continue to participate in the study. This will not affect your rights as a VHA patient.


If you withdraw this authorization, Dr. Buchheit and his research team will continue to use information about you that has been collected. No information will be collected after you withdraw the authorization.

As part of the study, we may disclose your information and medical and/or research records to the Office for Human Research Protections (OHRP), representatives of the USAMRMC (DOD), the VA Office of the Inspector General (OIG), the Office of Research Oversight (ORO), other government agencies, the Durham VAMC Institutional Review Board (IRB), and/or local Research Compliance Officers. We will not share any information with these groups outside the VHA unless they agree to keep the information confidential and use it only for the purposes related to the study. Any information shared with these outside groups may no longer be protected under federal law. If the sponsor receives identified information, it is then the sponsor, and not the VA, who is responsible for the security of the information. For compensation for participation in the study, Duke University will collect your name, address and social security number to process payment.

The VHA complies with the requirements of the Health Insurance Portability and Accountability Act of 1996 and its privacy regulations and all other applicable laws that protect your privacy. We will protect your information according to these laws. Despite these protections, there is a possibility that your information could be used or disclosed in a way that it will no longer be protected. Our Notice of Privacy Practices (a separate document) provides more information on how we protect your information. If you do not have a copy of the Notice, the research team will provide one to you.

I have read this authorization form and have been given the opportunity to ask questions. If I have questions later, I understand I can contact Dr. Buchheit at (919) 740-1099. I will be given a signed copy of this authorization form for my records. I authorize the use and disclosure of my identifiable information as described in this form.

The Paperwork Reduction Act of 1995 requires us to notify you that this information collection is in accordance with the clearance

 Department of Veterans Affairs		HIPAA Authorization for Release of Protected Health Information for Research Purposes	
Title of Study: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain			Version Date: 10/23/2013
Principal Investigator: Thomas Buchheit, MD			VAMC: Durham

requirements of section 3507 of the Act. We may not conduct or sponsor, and you are not required to respond to, a collection of information unless it displays a valid OMB number. We expect that the time expended by all individuals completing this form will average 2 minutes. This includes the time to read the instructions, gather the necessary facts and fill out the form. The purpose of this form is to specifically outline the circumstances under which we may disclose data.

The execution of this form does not authorize the release of information other than that specifically described. The information requested on this form is solicited under Title 38, U.S.C. The form authorizes release of information that you specify in accordance with the Health Insurance Portability and Accountability Act, 45 CFR Parts 160 and 164, 5 U.S.C. 552a, and 38 U.S.C. 5701 and 7332. Your disclosure of information requested on this form is voluntary. However if the information, including Social Security Number (SSN) (the SSN will be used to locate records for release) is not furnished completely and accurately, Department of Veterans Affairs will be unable to comply with the request.

SIGNATURE OF PARTICIPANT	Full SSN	DATE

Abbreviated Mini Mental State Exam

1. How old are you?

2. What year is it?

3. What is your date of birth?

4. What hospital are you in right now?

5. Do you know who the current president is?

6. Can you count down from 10 to 1?

Date

Yes No
Eligibility

If consented, Pt ID

Signed

More about Dr. Buchheit...



Dr. Buchheit has practiced pain medicine for over 10 years with a focus on nerve injury and post-amputation pain syndromes. In addition to his clinical and research duties at the Durham VAMC he has also recently been named Director of Duke Pain Medicine.

In summary...

We believe that if valproate medications like valproic acid are added to conventional pain management techniques such as local anesthetic infusion, patients may see a reduction in the frequency and severity of chronic pain after surgery and amputation.

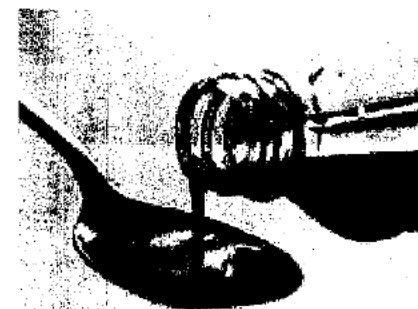
*To learn more about this study
please contact the Study Coordinator
at 919.286.0411, ext. 7372.*



RESEARCH STUDY

For:

Patients having amputation or surgery on an injured limb



Purpose

This research will test if an FDA approved valproate medication, valproic acid, will reduce pain after amputation or limb injury surgery. The ultimate goal of this research is to develop treatments that reduce chronic pain following limb injury or limb loss. Effective therapies would decrease the need for narcotic pain medications and their side effects such as tolerance and addiction.

Principal Investigator

Dr. Thomas Buchheit
Associate Professor of Anesthesiology
Duke University & Durham VAMC
595 LaSalle Street
Durham, NC 27705

More about the research...



Prevention of Post-Amputation Pain

Dr. Buchheit has received a 4-year research grant to study the effects of a medication to reduce the severity of nerve injury pain after surgery. This grant is sponsored by the *Department of Defense (DOD) Psychological Health and Traumatic Brain Injury Applied Neurotrauma Research Award with Clinical Trial Announcement*. The title of this grant is "Regional Anesthesia & Valproate Sodium for the Prevention of Chronic Post-Amputation Pain".

Eligibility

Study participants will be male and female veterans over the age of 18 who will be recruited from the population of patients at the Durham VA Medical Center requiring surgical amputation, stump revision or surgery for limb injury with neurologic damage.

Time Commitment

If enrolled in this study, blood samples will be collected from the participant on the day of surgery, 7 days after surgery and at 3-months during their follow up appointment. The total amount of blood collected is less than 6 tablespoons. Participants will also be asked to complete five questionnaires regarding pain levels at 1, 3 and 6 month follow-up appointments at the VA.

One half of participants will receive the study drug and one half will receive a placebo.

All participants will receive a check of \$50 after the 3-month follow-up appointment.

Benefit

If study findings are effective, long-term pain following amputation and nerve injury surgery may be reduced.



Background for this Study

After injury and surgery, most patients experience pain as they recover. Usually doctors use medications like narcotics, anti-inflammatory drugs and local anesthetics to treat this pain. More than 50% of patients who have an amputation, however, experience long-term chronic pain. Doctors in military and veteran hospitals have a great interest in this problem because they have realized that if patients have chronic pain, they may not be able to wear an artificial limb, they may not be able to walk well, and/or they may require chronic narcotic pain medicines. Researchers now believe that the best way to treat chronic pain is stop it before it starts.

We know that local anesthetics placed onto nerves work extremely well in preventing pain immediately after surgery. We also know that medications like valproates (valproic acid) work well in chronic pain and headache, but act slowly. We believe that the combination of these two medications (one quick-acting and one slow-acting) will work together to prevent chronic pain after amputation.

**DUKE UNIVERSITY &
DUKE UNIVERSITY HEALTH SYSTEM****IRB PERSONAL DATA DISCLOSURE FORM**

IRB Registry #: _____ Cost Object/ Fund Code #: _____

Compensation for participation in research (such as cash, check, or gift card) is considered taxable income to the research subject and Duke University is required in many cases to report this information to the Internal Revenue Service (IRS).

Non-employees

Research subject compensation to a non-employee of Duke University which exceeds \$600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

For minors or any aged subject: if subject is not working/not reporting his/her own taxes, then IRB Personal Data Disclosure Form needs to reflect parent/legal guardian signature & parent/legal guardian SS#.

Employees

Research subject compensation made to a Duke University employee at any time during the calendar year will result in a 1099 (Miscellaneous Income) form being issued to the employee and a copy sent to the IRS regardless of the total amount paid.

"I have agreed to be a subject in a research study conducted by [insert PI's name] with the IRB Registry # above. I understand that taking part in this study entitles me to receive the compensation described in the research consent form. It was explained to me that Duke University requires that I provide my name, mailing address, and social security number, as listed below, for Duke University Financial Services tax reporting purposes before compensation can be issued to me. I realize that if I do not provide this information I will not be compensated. I also understand that if I decide not to provide the requested information and I waive my right to compensation, I can still take part in the research study."

*Signature of Subject*_____
*Date of Signature*_____
*Printed Name of Subject*_____
Subject's Mailing Address (Please Print):

_____**Duke University Financial Services:**

The individual listed above is eligible for compensation as a result of participation in a Duke Medicine research study. If the payment type is denoted as "check" below, please issue and mail a check to the person named above at the address listed above. By signing this document, I verify that the person named above is participating, or has participated, in the research study cited above and is entitled to this compensation.

*Signature of Research Personnel*_____
*Date of Signature*_____
*Printed Name of Research Personnel*_____
Specify Payment Type (Check, Gift Card, Cash, Other) & Amount-----
Subject's Social Security Number: _____

If you do not want to provide your social security number, write your initials here _____. You can still take part in the research study as described in the consent form document, but you will not be compensated for your participation.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File? The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.

When Must I File? You must submit a completed, signed, and dated Statement:

A. Prior to:

- ♦ Initial review of a study protocol in which you are listed as Investigator,
- ♦ Continuing review of a study protocol in which you are listed as Investigator,
- ♦ Your being added as an Investigator to a study protocol,

OR

B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.

Note: The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.

Who Will Review My Statement? The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.

What if I Have Questions? Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

SEP 25 '14 10:38

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. **Complete all fields in Section I and III of the form.** Fields in Section II may be required depending on the responses in Section I.

IMPORTANT DEFINITIONS:

AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	Van De Ven, Thomas, J
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	Thomas.Vandeven@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY . With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

5. SPECIFIC TYPES OF FINANCIAL INTERESTS. A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? <i>Note: This does not include stock controlled through a diversified mutual fund or a blind trust</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? <i>Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>



- If you answered "yes" to any of the statements in Section I, you must respond to the associated question in Section II. Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name Van De Ven, Thomas, J

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name Van De Ven, Thomas, J

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

Add Another Company

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

Add Another Company

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.

TJV
(Initial)

I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).

TJV
(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.

TJV
(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

Thomas Van de Ven

(Signature)

Digitally signed by Thomas Van de Ven
DN: cn=Thomas Van de Ven, ou=, email=thomas.vandeven@va.gov, c=US
Date: 2014.06.19 16:59:23 -0400

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

Signature

Email

Telephone

I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:

Name Van De Ven, Thomas, J

PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File?	The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.
When Must I File?	<p>You must submit a completed, signed, and dated Statement:</p> <p>A. Prior to:</p> <ul style="list-style-type: none">◆ Initial review of a study protocol in which you are listed as Investigator,◆ Continuing review of a study protocol in which you are listed as Investigator,◆ Your being added as an Investigator to a study protocol, <p style="text-align: center;">OR</p> <p>B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.</p> <p><i>Note: The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.</i></p>
Who Will Review My Statement?	The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.
What if I Have Questions?	Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. Complete all fields in Section I and III of the form. Fields in Section II may be required depending on the responses in Section I.

IMPORTANT DEFINITIONS:

AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	BUCHHEIT THOMAS, MD
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	Thomas.Buchheit@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

SEP 25 '14 4:10:38

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY. With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name BUCHHEIT THOMAS, MD

5. SPECIFIC TYPES OF FINANCIAL INTERESTS.

A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? *Note: This does not include stock controlled through a diversified mutual fund or a blind trust*

Yes ☐

No ☒

B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? *Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States*

Yes ☐

No ☒



- If you answered "yes" to any of the statements in Section I, you **must respond to the associated question in Section II**. Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name BUCHHEIT THOMAS, MD

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name BUCHHEIT THOMAS, MD

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

Add Another Company

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

Add Another Company

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).


Name BUCHHEIT THOMAS, MD

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.


(Initial)


I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).


(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.


(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

 8/19/14
(Signature)

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

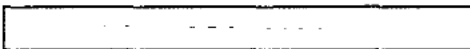
Signature



Email




Telephone



I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:



PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File? The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.

When Must I File? You must submit a completed, signed, and dated Statement:

A. Prior to:

- ◆ Initial review of a study protocol in which you are listed as Investigator,
- ◆ Continuing review of a study protocol in which you are listed as Investigator,
- ◆ Your being added as an Investigator to a study protocol,

OR

B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.

***Note:** The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.*

Who Will Review My Statement? The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.

What if I Have Questions? Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. **Complete all fields in Section I and III of the form. Fields in Section II may be required** depending on the responses in Section I.

SEP 25 '14 10:38

IMPORTANT DEFINITIONS:

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DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	RAGHUNATHAN, Karthik
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	karthik.Raghunathan@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

Name RAGHUNATHAN, Karthik

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY. With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name RAGHUNATHAN, Karthik

5. SPECIFIC TYPES OF FINANCIAL INTERESTS.		
A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? <i>Note: This does not include stock controlled through a diversified mutual fund or a blind trust</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? <i>Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>



- If you answered "yes" to any of the statements in Section I, you must respond to the associated question in Section II. Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name RAGHUNATHAN, Karthik

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

Add Another Company

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

Add Another Company

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

Name RAGHUNATHAN, Karthik

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.

KR

(Initial)

I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).

KR

(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.

KR

(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

karthik.raghunathan@va.gov

(Signature)

Digitally signed by karthik.raghunathan@va.gov
DN: cn=karthik.raghunathan@va.gov
Date: 2014.08.21 09:15:29 -04'00'

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

Signature

Email

Telephone

I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:

PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

- Why Must I File?** The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.
- When Must I File?** You must submit a completed, signed, and dated Statement:
- A. Prior to:
- ◆ Initial review of a study protocol in which you are listed as Investigator,
 - ◆ Continuing review of a study protocol in which you are listed as Investigator,
 - ◆ Your being added as an Investigator to a study protocol,
- OR
- B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.
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- Who Will Review My Statement?** The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.
- What if I Have Questions?** Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

SEP 25 '14 PM 10:38

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. Complete all fields in Section I and III of the form. Fields in Section II may be required depending on the responses in Section I.

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AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	SHORTELL, Cynthia, K.
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-681-2223
VA EMAIL	cynthia.shortell@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

Name SHORTELL, Cynthia, K.

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY . With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name SHORTELL, Cynthia, K.

5 . SPECIFIC TYPES OF FINANCIAL INTERESTS.

A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? *Note: This does not include stock controlled through a diversified mutual fund or a blind trust*

Yes ☐

No ☒

B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? *Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States*

Yes ☐

No ☒



- If you answered "yes" to any of the statements in Section I, you **must respond to the associated question in Section II.** Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name SHORTELL, Cynthia, K.

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name SHORTELL, Cynthia, K.

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

Name SHORTELL, Cynthia, K.

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.

CKS

(Initial)

I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).

CKS

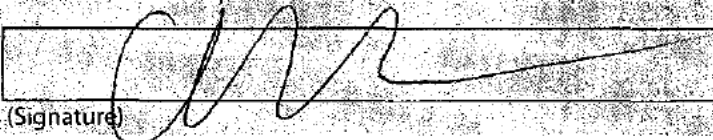

(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.

CKS

(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

 
(Signature)

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

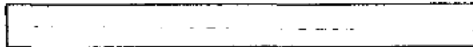
Signature



Email



Telephone



I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:



Name SHORTELL, Cynthia, K.

PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File? The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.

When Must I File? You must submit a completed, signed, and dated Statement:

A. Prior to:

- ◆ Initial review of a study protocol in which you are listed as Investigator,
- ◆ Continuing review of a study protocol in which you are listed as Investigator,
- ◆ Your being added as an Investigator to a study protocol,

OR

B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.

Note: The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.

Who Will Review My Statement? The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.

What if I Have Questions? Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

SEP 25 '14 04:10:38

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. **Complete all fields in Section I and III of the form. Fields in Section II may be required** depending on the responses in Section I.

IMPORTANT DEFINITIONS:

AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	HSIA, Hung-Lun (John)
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	Hung-Lun.Hsia@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY . With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name HSIA, Hung-Lun (John)

5. SPECIFIC TYPES OF FINANCIAL INTERESTS.

A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? *Note: This does not include stock controlled through a diversified mutual fund or a blind trust*

Yes ☐

No ☒

B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? *Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States*

Yes ☐

No ☒



- If you answered "yes" to any of the statements in Section I, you must respond to the associated question in Section II. Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name HSIA, Hung-Lun (John)

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name HSIA, Hung-Lun (John)

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

Name HSIA, Hung-Lun (John)

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.

HSIA

(Initial)

I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).

HSIA

(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.

HSIA

(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.

John HSIA 8/25/14
(Signature)

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

Signature

Email

Telephone

I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:

Name HSIA, Hung-Lun (John)

PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File? The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.

When Must I File? You must submit a completed, signed, and dated Statement:

A. Prior to:

- ♦ Initial review of a study protocol in which you are listed as Investigator,
- ♦ Continuing review of a study protocol in which you are listed as Investigator,
- ♦ Your being added as an Investigator to a study protocol,

OR

B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.

Note: The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.

Who Will Review My Statement? The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.

What if I Have Questions? Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. **Complete all fields in Section I and III of the form.** Fields in Section II may be required depending on the responses in Section I.

IMPORTANT DEFINITIONS:

AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	HOBBS, Juliann, C.
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	Juliann.Hobbs@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

SEP 25 10:03 AM '13

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY . With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name HOBBS, Juliann, C.

5. SPECIFIC TYPES OF FINANCIAL INTERESTS.

A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? <i>Note: This does not include stock controlled through a diversified mutual fund or a blind trust</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? <i>Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States</i>	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>



- If you answered "yes" to any of the statements in Section I, you **must respond to the associated question in Section II**. Only items for which you answered "yes" in Section I will be available in Section II.
- If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name HOBBS, Juliann, C.

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name HOBBS, Juliann, C.

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement


By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.


(Initial)

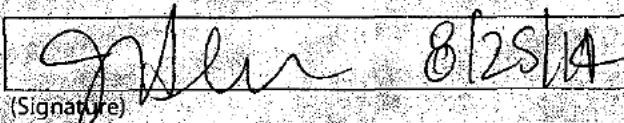
I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).


(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.


(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.


(Signature)

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

Signature

Email

Telephone

I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:

PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

Why Must I File? The duties and responsibilities of your position as a principal investigator, co-principal investigator, investigator (including a collaborator who has a VA appointment), study chair or site principal investigator (hereinafter "Investigators") require you to file a Research Financial Conflict of Interest Statement (Statement) to avoid involvement in a real or perceived conflict of interest. Federal employees are prohibited from participating personally and substantially in official VA matters affecting their own financial interest or those imputed to them. In addition, in research a real or perceived conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results, or reporting of research activities or findings. This Statement is to assist employees to avoid a conflict between their official duties and private financial interests or affiliations. See VHA Handbook 1200.13.

When Must I File? You must submit a completed, signed, and dated Statement:

A. Prior to:

- ◆ Initial review of a study protocol in which you are listed as Investigator,
- ◆ Continuing review of a study protocol in which you are listed as Investigator,
- ◆ Your being added as an Investigator to a study protocol,

OR

B. When you have a change in relevant information that requires you to change an answer on Section I of the Statement to "yes" or that changes the reason for a "yes" answer.

Note: The term "Investigator" includes: Principal Investigator (PI), Study Chair, Site PI, co-PI, or an Investigator, including a co-investigator or sub-investigator.

Who Will Review My Statement? The Financial Conflict of Interest Committee or Financial Conflict of Interest Administrator, with assistance from the Office of General Counsel (OGC) when necessary, is responsible for reviewing the Statement to determine whether there are any actual or perceived conflicts of interest. The Statement may be reviewed by other VA personnel only on an "as needed" basis when required by the responsibilities of their positions. The information you provide will be used only for legitimate purposes, and will not be otherwise disclosed unless authorized.

What if I Have Questions? Contact the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program or an OGC Deputy Ethics Official.

RESEARCH FINANCIAL CONFLICT OF INTEREST STATEMENT
Department of Veterans Affairs

INSTRUCTIONS: Complete this Statement to the best of your knowledge. Answering any question in the affirmative does not itself prevent you from conducting VA research or receiving VA funding. You will, however, need to provide additional information so that a determination can be made of how to best manage any conflict of interest that may be identified. Complete all fields in Section I and III of the form. Fields in Section II may be required depending on the responses in Section I.

IMPORTANT DEFINITIONS:

AFFECT THE FINANCIAL INTEREST - Means the possibility to impact, either positively or negatively, the value or amount of financial interest to any degree whatsoever.

CLOSE RELATIVE - An individual who is related as father, mother, son, daughter, brother, sister, uncle, aunt, first cousin, nephew, niece, father-in-law, mother-in-law, son-in-law, daughter-in-law, brother-in-law, sister-in-law, stepfather, stepmother, stepson, stepdaughter, stepbrother, stepsister, half-brother, or half-sister.

DEPENDENT CHILD - A son, daughter, stepson, or stepdaughter and who either is (i) unmarried, under age 21, and living in your house, or (ii) considered dependent under the U.S. tax code.

ENTITY - Any person, for-profit or non-profit organization, institution (including a university), corporation, partnership, or governmental agency (other than a Federal agency).

OUTSIDE EMPLOYER - An entity with which you serve as officer, director, trustee, general partner, or employee.

NAME (Last, First, Middle)	PYATI, Srinivas
DUTY STATION	DURHAM VAMC 558
TELEPHONE NUMBER	919-286-6938
VA EMAIL	Srinivas.Pyati@va.gov
NAME OF STUDY	Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
FACILITY PI	BUCHHEIT THOMAS, MD
SPONSOR OF STUDY	DEPARTMENT OF DEFENSE
FUNDING SOURCE	GRANT FROM THE DEPARTMENT OF DEFENSE TO DUKE UNIVERSITY MEDICAL CENTER

THIS IS A COOPERATIVE STUDIES PROGRAM ☐ Yes ☒ No

☐ I DO NOT HAVE AN APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☒ I HAVE A SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

☐ I HAVE A NON-SALARIED APPOINTMENT WITH THE UNIVERSITY AFFILIATE

SECTION I

1. INCOME AND COMPENSATION Do you, your spouse, dependent child or general partner receive income or other compensation (including non-Federal salary, consulting fees, honoraria, gifts, and in-kind compensation) from an entity (including the university affiliate) whose financial interests could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
2. BUSINESS RELATIONSHIPS. A. Current Relationships: Are you, your spouse, dependent child, general partner or parent serving, or seeking to serve, as officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee (paid or unpaid) with any entity (other than the Federal Government, but including the university affiliate) whose financial interest could be affected?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
B. Covered Relationships: Could this study affect the financial interest of you, your spouse, close relative, household member or general partner?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
C. Relationships in the Past Year: Have you, within the last year, served as an officer, director, trustee, general partner, agent, attorney, consultant, contractor or employee for any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
D. Business Arrangement or Agreements: Are you seeking, negotiating for, or do you have, any business arrangement or agreement, such as a future employment agreement, re-employment rights, consultant agreement, pending severance arrangement or retirement plan, with any entity whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
3. INTELLECTUAL PROPERTY. With respect to intellectual property that could be affected by this study, are you, your spouse, dependent child, general partner, or outside employer: (i) listed as the inventor on an invention disclosure or a patent application; (ii) the owner of any intellectual property; (iii) the holder of a license of a patent, copyright, software or other intellectual property; (iv) entitled to earn royalties now or in the future; (v) the author of written materials that are, or are going to be, commercialized; (vi) otherwise earning compensation from, or have a financial interest in, intellectual property (not covered elsewhere in this form); OR (vii) holding any other financial relationship not covered elsewhere in this form?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>
4. NON - PUBLICLY TRADED COMPANIES. Do you, your spouse, dependent child, or general partner have any stock, stock options, or other equity interest in a non-publicly traded company whose financial interest could be affected by this study?	Yes <input type="checkbox"/>	No <input checked="" type="checkbox"/>

Name PYATI, Srinivas

5. SPECIFIC TYPES OF FINANCIAL INTERESTS.

A. Publicly-Traded Companies: Do you, your spouse, or dependent child (in the aggregate) own or have an equity interest (stock ownership, stock options, etc.) valued at more than \$15,000 in a publicly-traded company or companies (aggregate value of all stocks in all such companies) whose financial interest could be affected by this study? *Note: This does not include stock controlled through a diversified mutual fund or a blind trust*

Yes ☐

No ☒

B. Sector Mutual Funds: Do you, your spouse or dependent child (in the aggregate) have equity holdings valued at more than \$50,000 in any sector mutual fund (or funds that concentrate in the same sector) whose holdings could be affected by this study? *Note: A sector mutual fund concentrates its investments in an industry, business, single country other than the United States, or bonds of a single State within the United States*

Yes ☐

No ☒



• If you answered "yes" to any of the statements in Section I, you must respond to the associated question in Section II. Only items for which you answered "yes" in Section I will be available in Section II.

• If you answered "no" to all statements in Section I, skip Section II, and proceed to Section III.

Name PYATI, Srinivas

SECTION II

1. INCOME AND COMPENSATION. If you answered yes in paragraph 1 of Section I, explain the source, value, and reason for the income or other compensation.

2. BUSINESS RELATIONSHIPS A. Current or Future Relationships. If you answered yes in paragraph 2.A. of Section I, provide: (i) relationship to you of person serving or seeking to serve, (ii) the name of the entity in which the person serves/seeks to serve, (iii) the type of business, and (iv) how the entity's financial interest could be affected by this study

B. Covered Relationships. If you answered yes in paragraph 2.B. of Section I, identify: (i) the relationship between you and the person whose financial interest could be affected by this study, (ii) how this person's financial interest could be affected by this study.

C. Relationships in Past Year. If you answered yes in paragraph 2.C. of Section I, provide: (i) name of the outside business, (ii) the type of business; (iii) your position with the outside business, and (iv) the date your relationship with the business ended.

D. Business Arrangement or Agreements. If you answered yes in paragraph 2.D. of Section I, provide: (i) name of entity with whom you are seeking, negotiating, or have an arrangement, (ii) type of business conducted by entity, (iii) brief description of the arrangement or agreement you are seeking, negotiating, or have with the entity, and (iv) description of the entity's relation to this study.

3. INTELLECTUAL PROPERTY . If you answered yes in paragraph 3 in Section I, identify (i) what you, your spouse, dependent child, general partner, or outside employer has, and (ii) how it could be affected by this study.

Name PYATI, Srinivas

4. NON-PUBLICLY TRADED COMPANIES. If you answered yes in paragraph 4 of Section I, provide additional information below.

Name of Company

Type of Equity Interest

Describe the nature of the company and how its financial interest could be affected by this study.

Add Another Company

5. SPECIFIC TYPES OF FINANCIAL INTERESTS

A. Publicly Traded Companies. If you answered yes in paragraph 5.A. of Section I, provide additional information below for each affected company.

Name of Company

Type of Equity Interest

Value of Equity Interest

Describe the company's business and how it is related to your area of research.

Add Another Company

B. Sector Mutual Funds. If you answered yes in paragraph B of Section I, identify the names of the relevant fund(s).

Name PYATI, Srinivas

SECTION III

All Investigators must read, initial, and sign the acknowledgement below. Submit completed Statement to the facility research Financial Conflict of Interest Administrator or Committee designated by the facility's Director as responsible for the facility's research conflict of interest program: a) in sealed envelope, b) as attachment to encrypted message, or c) by uploading to FCOI Committee/Administrator secure website, if applicable.

Acknowledgement

By signing below, I certify that, to the best of my knowledge and belief, all of the information on this Statement is true, correct, and complete as of the date of my signature below, and I authorize the reviewer of this Statement to share the information contained herein with the appropriate Research and Development Committee and sub-committees on a need-to-know basis.


(Initial)

I understand that false or fraudulent information on this Statement may be grounds for not approving the research proposal and may be punishable by fine or imprisonment (U.S. Code, Title 18, section 1001).


(Initial)

I agree to update relevant information, contact my supervisor, and notify the R&D Committee or appropriate sub-committee with respect to any new financial interest(s) that requires me to change an answer in Section I of this Statement to "yes" or that changes the reason for a "yes" answer.


(Initial)

I understand that in addition to the disclosures required in this Statement, I am subject to the criminal conflict of interest statutes at Title 18 of the United States Code, Chapter 11, and the Executive Branch Standards of Conduct at Title 5 of the Code of Federal Regulations, Part 2635. Violation of these provisions may be sanctioned by civil and criminal penalties, as well as employment-related discipline such as removal or suspension.


(Signature)

09/09/2014

For Use by Reviewing Official Only

On the basis of information contained in this report, I conclude that the filer is in compliance with applicable laws and regulations, except as noted in the "comments" box below.

Signature



Email



Telephone



I am the Facility Financial Conflict of Interest Administrator or Committee member authorized to certify Statements

I am an OGC Deputy Ethics Official

Comments:



PRIVACY ACT STATEMENT

Title I of the Ethics in Government Act of 1978 (5 U.S.C. App.), Executive Order 12674, and 5 CFR 2634, Subpart I, of the Office of Government Ethics regulations require the reporting of this information. The primary use of the information on this form is for review by the VHA R&D Committee or appropriate sub-committee, and when necessary the VA Office of General Counsel, to determine compliance with applicable Federal conflict of interest laws and regulations and the impact of any real or perceived financial conflicts of interest on VA research. Additional disclosures of information in this report may be made:

- (1) to other VA research review committees and VA officials responsible for the approval or funding of research protocols;
- (2) if there is an indication of a violation or potential violation of law, whether civil, criminal or regulatory in nature and whether arising by general statute or particular program statute, or by regulation, rule or order issued pursuant thereto, to the appropriate Federal, State or local agency charged with the responsibility of investigating or prosecuting such violation or charged with enforcing or implementing the statute or rule, regulation or order issued pursuant thereto;
- (3) to qualified reviewers for their opinion and evaluation of a proposal as part of the application review management inspections; and
- (4) to the Department of Justice (DOJ) upon official request in order for VA to respond to pleadings, interrogatories, orders or inquiries from DOJ and to supply to DOJ the information to enable DOJ to represent the U.S. Government in any phase of litigation or in any case or controversy involving VA.

Failure to file or report information or the falsification of required information may subject you to disciplinary action by the VA or other appropriate authority. This may include limitation on or revocation of the privilege to conduct VA-approved research. It may also be subject to criminal prosecution.

Williams, Shelina

From: Zinn, Sandra DURVAMC
Sent: Thursday, July 03, 2014 6:42 PM
To: Williams, Shelina
Cc: Rhodes, Virginia DURVAMC
Subject: ATTN: Mandatory Update of all Human Informed Consent Documents for DVAMC studies

To All Human Research Study Staff:

The IRB has determined that all active studies still enrolling human subjects using an informed consent (IC) document must upgrade to the newest "FAQ-style" IC form over the coming year. This is effective after **July 28th**, the deadline for items for the August IRB meeting. After that date, each submission for Annual (continuing) Review (and any amendments that affect the IC form or HIPAA authorization) should include the newest versions of the consent and HIPAA authorization, as well as the current (old) version for comparison during IRB review. Your submission will not be reviewed until these new versions are provided to the Research Office.

Please note that any studies with ongoing enrollment using the *2009 combined ICF/HIPAA authorization* form must **remove** the HIPAA authorization language from the consent document and submit a separate new HIPAA authorization form to accompany their new informed consent document.

The new templates for the informed consent and HIPAA authorization are attached (G_ICF_Template_2014-06-12 and G_HIPAA_Authorization_Template_2014-06-12). These documents are also available on the S drive and the Research Program's website.

SUMMARY:

- All consent forms to be upgraded to latest template *if ongoing enrollment*
- Applies to all submissions after **7/28/14**
- **Both** ICF and HIPAA authorization documents are required at Annual Continuing Review
- Submit both old & new versions
- HIPAA **waiver** documents do NOT have to be submitted

Please help spread the word! **Thank you** for all you do to help us maintain an exemplary Human Research Protections Program despite the regulatory mania. You may contact Shelina Williams (x5170), Virginia Rhodes (x4726) or Terrie Northcraft (x7293) if you have questions.

Regards,
Sandra Zinn, PhD
DVAMC IRB Chair

The ICF and HIPAA Authorization template dates are:

ICF Template: 2014-06-12

HIPAA Authorization Template: 2014-06-12

Mary M Kirkley

From: Wells Roark, Lisa L CIV USARMY MEDCOM USAMRAA (US)
<lisa.l.wellsroark.civ@mail.mil>
Sent: Thursday, October 02, 2014 10:06 AM
To: Juliette Lee-Campbell
Cc: Thomas Buchheit, M.D.; Thomas Van De Ven, M.D.; Mary M Kirkley; Zarrin T Brooks; Henry, Patricia A CTR USARMY MEDCOM CDMRP (US); Grants & Contracts E-Mail; Wells Roark, Lisa L CIV USARMY MEDCOM USAMRAA (US)
Subject: RE: Revised SOW & Budget for A-17886.b HRPO Initial Approval Memorandum (Proposal Log Number PT110575, Award Log Number W81XWH-12-2-0129) (UNCLASSIFIED) (Duke SPS# 187092)
Attachments: SOWrevised8.8.14.pdf; 8.5.14rebudget.revision.pdf

Good morning Ms. Lee-Campbell,

Your request to revise the SOW and budget has been approved. A modification to the award is not required, however, the attached documents will be included in the award file for future reference.

Please note that no additional funding will be provided for the changes.

Regards,

Lisa L. Wells Roark
Contract Specialist
USAMRAA
820 Chandler Street
Fort Detrick, MD 21702-5014
Phone: 301-619-2086
Email: lisa.l.wellsroark.civ@mail.mil

From: Juliette Lee-Campbell [mailto:juliette.lee-campbell@duke.edu]
Sent: Thursday, October 02, 2014 9:58 AM
To: Wells Roark, Lisa L CIV USARMY MEDCOM USAMRAA (US)
Cc: Thomas Buchheit, M.D.; Thomas Van De Ven, M.D.; Mary M Kirkley; Zarrin T Brooks; Henry, Patricia A CTR USARMY MEDCOM CDMRP (US); Grants & Contracts E-Mail
Subject: FW: A-17886.b HRPO Initial Approval Memorandum (Proposal Log Number PT110575, Award Log Number W81XWH-12-2-0129) (UNCLASSIFIED) (Duke SPS# 187092)

Dear Ms. Wells Roark:

By way of this email we would like to confirm that the Office of Research Administration in the Duke School of Medicine endorses the above documents submitted on behalf of our PI, Dr. Thomas Buchheit by Ms. Mary Kirkley.

In the future we will make every effort to have these submissions sent directly through this office to you, as per your request.

**Duke University Medical Center/Durham Veterans Affairs Medical
Center**

Department of Anesthesiology

Clinical Research Study Protocol

TITLE

Regional Anesthesia and Valproate Sodium
for the Prevention of Chronic Post-Amputation Pain

PRINCIPAL INVESTIGATOR

Thomas Buchheit, MD

Protocol Version

VAvalproateProtocol_V28_Duke 3.docx

Protocol version date

July 24, 2014

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INVESTIGATORS

Principal Investigator:

Thomas Buchheit, MD

Associate Professor

Department of Anesthesiology, Duke University Medical Center

DUMC Box 3094, Durham, NC 27710

Co-Investigators:

Thomas Van de Ven, MD, PhD

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DUMC Box 3094, Durham, NC 27710

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DUMC Box 3094, Durham, NC 27710

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Assistant Professor

Department of Anesthesiology, Duke University Medical Center

Durham Veterans Affairs Medical Center, 508 Fulton St, Durham, NC 27705

Karthik Raghunathan, MD

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Durham Veterans Affairs Medical Center, 508 Fulton St, Durham, NC 27705

Srinivas Pyati, MD

Assistant Professor

Department of Anesthesiology, Duke University Medical Center

Durham Veterans Affairs Medical Center, 508 Fulton St, Durham, NC 27705

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PROTOCOL SUMMARY

PURPOSE

This protocol is designed to test the efficacy of an FDA approved medication (valproate or valproic acid) for the prevention of chronic neuropathic and post-amputation pain. The ultimate goal of this research is to develop strategies to reduce chronic pain following limb injury or limb loss, thereby decreasing the need for narcotic pain medications and their potential side effects such as opioid tolerance and addiction. An effective preventive strategy would additionally reduce medication side effects such as sedation and confusion that are of particular importance in individuals with traumatic brain injury (TBI) and cognitive deficits.

Regional anesthesia catheters are commonly used in the postoperative period and provide excellent control of acute post-amputation pain. However, their use does not appear to be effective in reducing the incidence of chronic pain.¹ In a complementary manner, valproates have demonstrated efficacy in the treatment of chronic neuropathic pain and neuroprotection following chemotherapy and injury.²⁻⁴ In this research project we will determine whether the addition of oral valproate (valproic acid) to regional anesthesia reduces the incidence of chronic neuropathic and post-amputation pain. Furthermore, we will analyze the underlying inflammatory and epigenetic modifications using mechanistic studies nested within the clinical trial.

RESEARCH DESIGN

This is a randomized, double-blinded, placebo-controlled trial to test the efficacy of valproic acid (VPA) in reducing the incidence of chronic neuropathic and post-amputation pain. It is additionally a nested, observational study of the epigenetic modifications that occur in the transition from acute to chronic pain.

METHODOLOGY / TECHNICAL APPROACH

420 patients (210 patients at Duke University Medical Center (DUMC)/ Durham Veteran's Affairs Medical Center (DVAMC) and 210 at Walter Reed National Military Medical Center) will be enrolled. Subjects at the DUMC/DVAMC will be recruited from the surgical clinics and the anesthesia pre-operative clinic. After screening and enrollment, the study medication (VPA or placebo) will be administered for a total of 7 days (day of surgery and 6 days following surgery) or until the time of discharge from the hospital. Longitudinal follow-up will occur at Duke University either in the Pre-operative Clinic or the Pain Clinic that is managed by the principal investigator. Outcomes for patients in the intervention arm will be compared with those managed with the current institutional standards of care including regional anesthesia catheter infusions.

Research blood samples will be collected preoperatively, postoperatively (at the completion of study drug intervention), and at Clinic follow-up (approximately 3 months) for analysis of metabolic changes, epigenetic modifications, and gene expression alterations. All samples will be de-identified and subsequently studied in our laboratory in the Snyderman Genome Sciences Research Building and several core facilities at Duke. We will also use a 3rd party metabolomics facility, Metabolon, Inc. in Raleigh, to measure plasma metabolomic differences between case and control subjects. Metabolon will receive completely de-identified plasma samples for these assays. Quest Diagnostics may be used for analysis of valproate levels at the end of study drug administration.

INTRODUCTION

LITERATURE REVIEW AND BACKGROUND

Perioperative local anesthetic infusion at the peripheral nerves has been studied in an effort to reduce the incidence of chronic post-amputation pain. Although these techniques have been shown to be successful in reducing the burden of acute pain, their use, unfortunately, does not appear to reduce the burden of chronic pain.¹ Our ongoing treatment limitations for chronic pain after amputation and nerve injury necessitate the search for more effective preventive methods.

Just as acute pain investigators are turning to multimodal analgesic techniques to improve outcomes, we will employ a multimodal technique utilizing a common intervention for acute pain (regional anesthesia catheter infusion) and an FDA approved medication for headache and neuropathic pain (valproic acid). We hypothesize that blocking these mechanisms simultaneously will significantly reduce the incidence of chronic pain in these patients. We will analyze clinical outcomes and delineate the underlying epigenetic mechanisms involved using studies nested within a clinical trial. In addition to these important clinical outcome measures, we will determine the extent to which the effectiveness of VPA is mediated via epigenetic changes of differential DNA methylation in pain pathway genes. This study is of critical importance given the limitations of current opioid-based therapies and the need for new classes of medications.

Valproates are of particular interest given their success with long-term clinical use,³ and their established effectiveness in the management of neuropathic pain.^{2,5} We believe that the epigenetic effects of valproates (DNA methylation/demethylation) will cause this class of medications to demonstrate effectiveness in preventing the transition from acute to chronic pain.⁶ These medications have been shown to induce demethylation of Reelin, a glycoprotein synthesized by GABAergic neurons of the central nervous system⁷ and important for N-methyl-D-aspartate (NMDA) receptor function,⁸ sensory processing, and the development of hypersensitivity.^{9,10} Following injury, there is a clear phenotypic switch in the neurologic system of patients who develop chronic pain. Epigenetic modifications are known to play a role in the development of disease states such as cancer,¹¹ neurodegenerative disease,¹² and chronic pain.¹³ We believe that similar epigenetic alterations are responsible for the development of chronic pain after nerve injury and amputation.

JUSTIFICATION FOR STUDY

It has been estimated that between 51% and 85% of patients who have undergone amputation experience significant phantom or residual limb pain.^{14,15} Chronic pain in this population has a significant impact on rehabilitation, substance abuse, and depression. Although medication therapies such as tricyclic antidepressants, anticonvulsants and opioids are considered first-line therapy, and surgical techniques such as dorsal root entry zone lesions (DREZ), sympathectomies, and spinal cord stimulation have been used, there is currently little evidence to support the efficacy of these techniques.¹⁶ Our inability to consistently treat chronic neuropathic and post-amputation pain further supports the critical need for effective preventive strategies.

INTENDED / POTENTIAL USE OF STUDY FINDINGS

The intended use of the findings of this study is to determine if a commonly used, FDA approved medication for neuropathic pain and seizure disorder (valproic acid) can reduce the incidence of chronic pain following amputation, stump revision, or surgery for limb injury with neurologic damage. Given the unique pharmacologic properties (epigenetically active anti-convulsant) of valproic acid (VPA), we believe that it may demonstrate efficacy in preventing the transition from acute to chronic pain where other commonly used anti-convulsants, such as gabapentin, have failed.¹⁷ This trial seeks an easily administered oral therapy that is effective, inexpensive, and most importantly, a non-narcotic solution to chronic pain after injury. If effective, this project will have a direct and immediate impact upon the thousands of individuals who undergo traumatic and/or surgical amputation as well as those with chronic neuropathic pain following limb injury.

STUDY DESIGN / LOCATIONS

This study will be a prospective, randomized, double blind, placebo-controlled clinical trial of oral valproic acid for amputation, stump revision, and surgery for limb injury with neurologic damage. 420 patients will be enrolled over 4 year duration at multiple sites. We plan to enroll 210 patients (50%) at the DUMC/DVAMC. The study will take place in the preoperative clinics, surgical wards, intensive care unit and the Pain Clinic. Patients will receive standard regional anesthesia catheters and anesthetic management, and will be randomized to receive either oral placebo or oral valproic acid (250mg) on the day of surgery and then three times per day for 6 days post-operatively or until the time of discharge from the hospital. Intervention arm patients will be compared with patients treated with current institutional standards of care including regional anesthesia (to include the use of both peripheral nerve catheters and epidural catheters).

This study is registered at ClinicalTrials.gov and DUMC will be added as a recruitment site once IRB approval is obtained. The primary hypothesis is that fewer patients treated with valproic acid will have significant chronic pain at the 3 month evaluation point. In addition to the clinical trial, there will be a nested observational study to evaluate the metabolic changes, epigenetic modifications (DNA methylation), and gene expression alterations that occur in the transition from acute to chronic pain, and the extent to which the effectiveness of VPA is mediated through epigenetic changes in pain pathway genes.

OBJECTIVES

Our objectives of this study are to simultaneously test the effectiveness of an FDA approved medication for the prevention of post-amputation chronic pain, and to further delineate the underlying inflammatory and epigenetic mechanisms that lead to the development of chronic pain after nerve injury.

HYPOTHESES AND QUESTIONS

Hypothesis 1: The use of combined regional anesthesia and oral valproic acid (VPA) in surgical limb-injury patients will decrease the incidence of chronic neuropathic and post-amputation pain.

Goal 1: In a multi-center, blinded randomized placebo-controlled clinical trial, we will determine if oral VPA added to regional anesthesia and standard perioperative management will reduce the incidence of neuropathic and post-amputation pain when compared with regional anesthesia alone.

Hypothesis 2: The transition from acute to chronic pain is mediated via epigenetic mechanisms (differential DNA methylation) in genes involved in nociception. These epigenetic changes are modifiable with the use of VPA, a known inhibitor of DNA methylation.

Goal 2: We will analyze the DNA methylation patterns of patients with different types of neuropathic and post-amputation pain and determine the way they are altered by VPA. We will confirm the functional relevance of these modifications using circulating leukocyte gene expression signatures.

GENERAL APPROACH

The following study activities will occur in the sequence noted in the timeline below:

- a. Advertising for the study will occur in the surgical and pre-anesthesia clinics.
- b. Screening for possible study candidates will be performed in the clinics and the hospital ward as dictated by patient care needs. An IRB waiver for screening of patients will be obtained prior to study commencement.
- c. Patients who choose to enroll will have consent and HIPAA authorization performed preoperatively in a setting dictated by patient care and comfort. In this location (typically the pre-anesthesia clinic or hospital ward) the patient interview, medical record review, and study questionnaires

will be completed. A limited clinical exam (testing for level of sedation and neuropathic pain) will also be performed. After transfer to the pre-operative area for surgery, a blood sample will be drawn at the same time an intravenous line is placed for the conduction of anesthesia.

d. Study drug will be administered preoperatively after blood sample is taken. Follow-up observations and study drug administration will occur on the surgical ward or the intensive care unit, depending on the level of care dictated by standards of perioperative anesthetic and surgical management.

e. A mail-out survey will be performed at 1 month for symptom assessment (Between 3 and 6 weeks) followed by a telephone call by a member of the study team to verify if the mailed questionnaires were received and to document any adverse events since the time of discharge from the hospital and to confirm that a month 3 follow-up visit was scheduled. We will additionally ask the patient if they desire only a “study visit” at 3 months or a “study visit” and an appointment for clinical care/pain management to make sure we are optimally caring for the patient.

f. Two patient appointments (3 month (10-14 weeks) and 6 month (22-26 weeks), post-op) will be made Duke University Medical Center prior to discharge from the hospital. If a patient misses the month 3 appointment, he/she will be called to reschedule the appointment.

g. Phenotype adjudication by an expert panel will be performed for two time periods: study enrollment and at 3 month follow-up in the pain clinic.

DESIGN

AUDIENCE AND COST BENEFIT

This study will enroll individuals who require amputation or limb surgery secondary to trauma or chronic medical illness. The research is designed to have immediate clinical applicability for these populations. Since we are employing a currently available, inexpensive and FDA approved medication, this study protocol could immediately be deployed to a more general population undergoing amputation surgery for minimal cost. If effective, this protocol will also provide long-term financial savings since it would reduce requirement for long-term medical management.

STUDY TIME LINE

Study Procedures	Pre-op Evaluation	Day of Surgery	Post-Op Days 1-5	Post-Op Day 6 (End of Study Drug)	Follow-up 1 month	Follow-up 3 months	Follow-up 6 months
Screening	X						
Informed Consent	X						
Study Enrollment	X						
Randomization	X						
Symptom Questionnaires	X				X	X	X
Depression Questionnaire	X						
Daily Assessment Questionnaire	X		X	X	X	X	X
Sedation Assessment Questionnaire	X		X	X			
Amputation Questionnaires (if patient is amputee)	X					X	X
Study Drug Administered		X (2nd)	X	X			
Physical Exam	X					X	X
Research blood sample: P100, Paxgene RNA, Paxgene DNA		X (1st)		X		X	
Clinical blood sample: CBC, Liver panel (AST, ALT, Alk Phos, Bilirubin)				X		X	
Follow-up Phone Call					X	X	
Phenotype Adjudication	X					X	
VPA level				X			

STUDY POPULATION

This research will take place over 4 years at multiple sites. Study participants will be individuals age 18 and older, who will be recruited from the population of patients requiring surgical amputation, stump revision, or surgery for limb injury with neurologic damage secondary to trauma or chronic medical disease. The study will mirror the racial and ethnic characteristics of individuals with these injuries, consistent with the pragmatic nature of this trial. Race, ethnicity and sex will not be used as criteria to include or exclude patients in the study.

INCLUSION CRITERIA

Individuals, age 18 years and older presenting for amputation, stump revision, or surgery for a limb injury with neurologic damage will be eligible for this study. Neurologic damage will be defined clinically by the investigator as evidence of sensory or motor deficits consistent with injury to a major nerve.

EXCLUSION CRITERIA

1. Severe Traumatic Brain Injury (Diagnosis of traumatic brain injury resulting in documented, permanent or prolonged cognitive deficits that would preclude participation in the study)
2. Significant cognitive deficits or dementia of any cause as noted in the medical record. Prior to enrollment patients will be screened in person using an abbreviated version of the Mini-Mental Status Exam (MMSE) utilized to minimize patient burden and time. If more than two questions are answered incorrectly, the patient will be excluded from the study.

3. Patient has a designated Legally Authorized Representative (LAR)
4. Substantial hearing loss without alternative means of communication
5. Documented spinal cord injury with permanent or persistent deficits
6. Under age 18 or a legal Minor
7. Current pregnancy or lactation
8. Cirrhosis with evidence of decompensation: coagulopathy INR >1.3, thrombocytopenia with platelets <100,000, ascites or hepatic encephalopathy
9. Current therapy with valproic acid or other valproates, coumadin, chlorpromazine and olanzapine
10. Current diagnosis of seizure disorder requiring anti-epileptic medication
11. Current therapy with tricyclic antidepressants (eg: amitriptyline, nortriptyline, imipramine, desipramine) at doses greater than 50mg/day
12. Is currently taking zidovudine
13. Current diagnosis of malaria requiring anti-malaria medication (such as mefloquine and chloroquine)
14. Is currently taking monoamine oxidase inhibitors (MAOI)
15. Allergy to valproates or valproic acid
16. End-stage renal disease requiring dialysis
17. Contraindication to, or refusal of, regional anesthesia catheter

ESTIMATED NUMBER OF PARTICIPANTS

With an enrollment of 420 patients, we anticipate a 10% drop-out rate at 3 months secondary to death and loss to follow up. Thus 378 evaluable patients (189 patients in each arm) at 3 months after surgery will be included in this study. We anticipate enrolling 50% of the study subjects (210 subjects) at the DUMC/DVAMC with a recruitment rate of 5-6 subjects per month, over a 36-month duration.

ENROLLMENT

Subjects will be identified from the elective surgical schedules, the surgical clinics and the anesthesia preoperative clinic in addition to direct patient inquiry secondary to advertising at the DUMC/DVAMC, chosen by appropriate operative procedure. CPRS/Maestro Care records will be screened to evaluate for inclusion/exclusion criteria. Protected Health information (PHI) will be used to screen for eligibility but will not be recorded, except in the screen log, which will be in a password protected file on the shared drive of respective institutions, with limited access. Surgeons will be contacted to obtain permission to speak with potential subjects; a member of the study team will share brief study information with the provider prior to approaching any subject. Once the surgeon, primary care provider or caregiver provides the patient with an introduction to the study, and the patient agrees to meet, the study team member will approach to obtain informed consent. This will occur during their surgical clinic visit (as part of their anesthetic preoperative assessment) or during their hospitalization. This screening process will be performed by key study personnel. Since we are obtaining informed consent during the pre-operative evaluation period, we will give patients ample time to consider the study risks and benefits, and discuss options with family members or other concerned individuals prior to enrolling. They will then have the opportunity to turn down participation in the study without difficulty. If after speaking with the potential subject and he/she would not like to participate in the study, we would destroy all hard copy information by shredding.

Potential subjects who have undergone initial computer screening will then be interviewed in person to receive an explanation of the study and determine patient interest in participation. If the patient is interested in participation, they will be asked six questions from the Mini Mental Status Exam (MMSE) to confirm adequate cognition. If greater than two questions are answered incorrectly, they will be excluded from the study.

Subjects will receive a \$50 check for their participation in this study after the 3 month follow-up visit.

CONSENT PROCESS

General approval for study participation will be obtained from appropriate surgical teams prior to the start of enrollment. Subject's permission to be approached by research personnel will be obtained from the primary medical team involved with the patient, before the research personnel discusses the study with a potential subject. A member of the investigative team (clinical research coordinator or physician) will be responsible for explaining the study to the patient and answering questions. If enrolled at the DVAMC, a clinical warning will be entered in the patient record in CPRS; If enrolled at Duke University Medical Center, a research note will be made in Maestro Care; the patient will then be randomized to receive either placebo or active drug (valproic acid) prior to their surgery.

Since traumatic brain injury, severe cognitive deficits and dementia are exclusion criteria, we do not anticipate mental capacity difficulty in understanding the consent process secondary to these diagnoses. Additional safeguards will be taken to avoid obtaining informed consent during times of physical stress, emotional stress or when patients are sedated with medications. As only mentally competent patients without a history of significant traumatic brain injury, significant cognitive deficits, or significant dementia will be included in this study, we do not anticipate the need for Legally Authorized Representatives. A patient who has a designated LAR will be considered excluded for this research project.

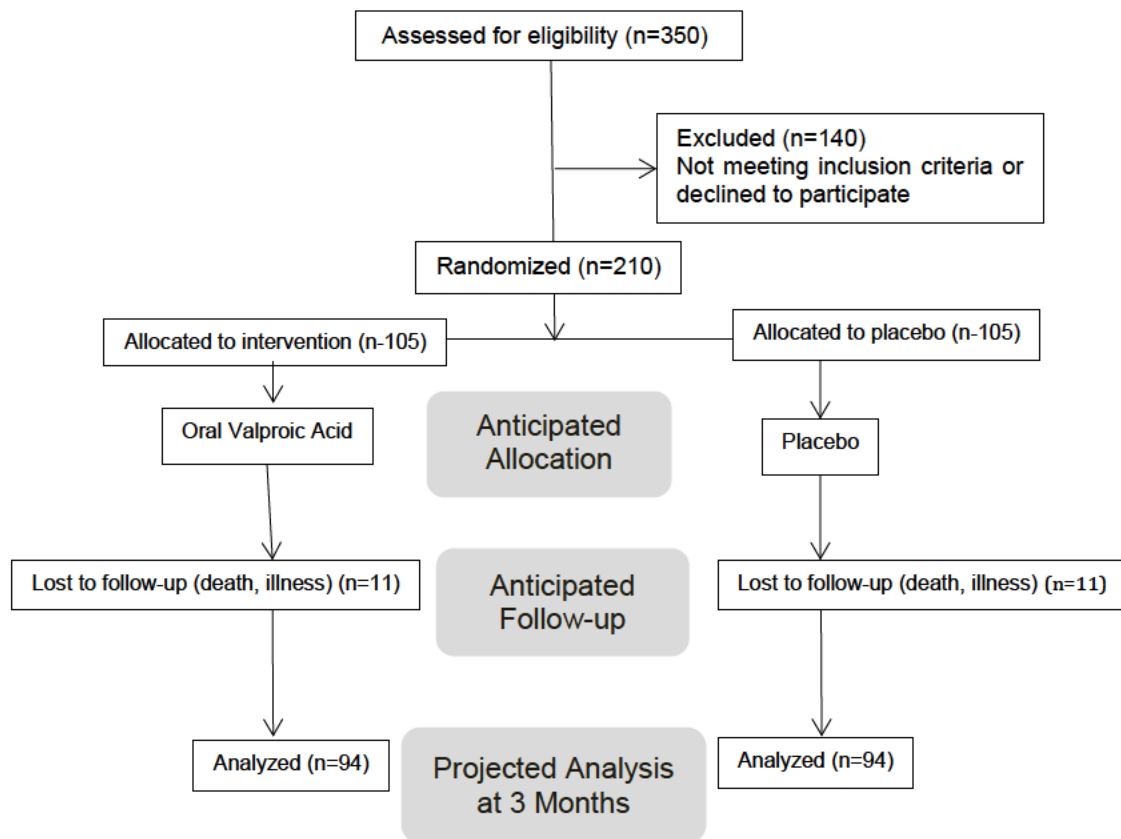
Subjects' understanding of the consent process will be enhanced in the following ways:

- Avoidance of hurry and rushing during the consent process
- Use of appropriate (6th grade) language in the consent documentation, in line with accepted standards for the DUMC/DVAMC Institutional Review Board.
- Consent will only be requested at a time when the subject is not obviously distressed or in severe pain.
- Consent documents will be fully compliant with the respective institution's guidelines for genetic research.

How may subjects withdraw from the study?

If a subject withdraws (discontinues participation) from the study, the investigator will retain and analyze already collected data relating to the subject and will not seek any further collection of data, PHI or blood samples from the subject; unless the data concerns an adverse event related to the study. If such an adverse event occurs, the entire medical record will be reviewed and all data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be kept. The subject can request that their data not be used and that the investigator excludes his/her data from any analysis.

DUKE UNIVERSITY MEDICAL CENTER/DURHAM VA MEDICAL CENTER RANDOMIZATION CHART



VARIABLES / INTERVENTIONS

STUDY DATA

The following information will be collected by reviewing the patient's medical chart in combination with a patient interview as follows:

- Abbreviated Mini-Mental Status Exam Questions (pre-enrollment patient interview)
- Demographics (name, address, telephone number, gender, ethnicity/race, age, Body Mass Index) (from the chart)
- Significant medical and surgical history (from the chart)
- Current narcotic medication dosage and total daily morphine equivalency (from the chart and patient interview)
- Current use of non-narcotic medications (anticonvulsants, tricyclic antidepressants, beta-blockers, non-steroidal anti-inflammatory medications, corticosteroids or fish oil supplements) (from chart)
- History of PTSD (from the patient chart)
- History of depression (from the chart and patient interview) Pain scales (from the patient interview)

DEPRESSION QUESTIONNAIRE

To be completed at time of study enrollment.

- Patient Health Questionnaire-2 (PHQ-2) (from the patient interview)

DAILY ASSESSMENT QUESTIONNAIRE

To be completed at time of study enrollment, during study drug administration, and subsequently at 1, 3 and 6 months:

- Defense and Veterans Pain Rating Scale (DVPRS) (from the patient interview)

SEDATION ASSESSMENT QUESTIONNAIRE

To be completed at time of study enrollment and during study drug administration:

- Richmond Agitation Sedation Scale (RASS) (from the patient interview)

SYMPTOM QUESTIONNAIRES

To be completed at time of study enrollment, 1, 3 and 6 months:

- Brief Pain Inventory (BPI) (from the patient interview)
- Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) (from the patient interview)

To be completed at time of study enrollment, 3 and 6 months:

- Complex Regional Pain Syndrome and Neuroma Questions at enrollment, 3 and 6 months (from the patient interview)

AMPUTATION QUESTIONNAIRES

To be completed at study enrollment, if patient has had prior amputation on the limb pending surgery, and at the 3 and 6 month follow-up visits for all patients who have undergone amputation:

- Phantom, Residual Limb Pain, and Prosthesis Questions (from the patient interview)

ANALYTIC TESTS

Blood Sample Collections

The information below outlines the timeframes for blood collection and lab supplies to be used. Clinical blood samples will be collected and analyzed in the DUMC/DVAMC Clinical Laboratory. Research blood samples will be collected and analyzed using the below noted protocols.

Day of Surgery

A research blood sample of 22ml (less than 1.5 tablespoons) will be collected from subjects for plasma, RNA and DNA.

Completion of Study Drug

The second blood draw of 34ml (approximately 2 tablespoons) will be performed for research analysis (plasma, RNA and DNA), and clinical analysis (liver function tests: Aspartate aminotransferase [AST], Alanine Aminotransferase [ALT], Alkaline Phosphatase, bilirubin, complete blood count (CBC) and VPA level. It will be obtained at the completion of the trial medication administration. If liver function tests and complete blood count have been performed within 24 hours of anticipated study labs, these will not be

duplicated.

Approach to Additional Analgesic Medications

Given the pragmatic nature of this trial, we anticipate that patients will be on multiple other analgesic regimens and may have medications changed or adjusted during the course of treatment. These medication adjustments will proceed as per the standard of care for the respective medical center. If tricyclic antidepressant (TCA) medications are increased above 50mg during the time of study drug administration, a TCA drug level will be obtained. If the drug level is greater than 400ng/ml or the patient appears to be experiencing drug-related side-effects, the TCA will be reduced to the original dose or discontinued.

3 Month Follow-up

The third and final blood draw of 30ml (approximately 2 tablespoons) will again be performed for research analysis (plasma, RNA and DNA), and clinical analysis (liver function tests: Aspartate aminotransferase [AST], Alanine Aminotransferase [ALT], Alkaline Phosphatase, bilirubin, and complete blood count (CBC). These will be taken during the 3 month follow up appointment. Time of day and duration of pre-sample fasting will be collected to control for any potential interaction with circadian rhythms and fasting status.

At the 3 month follow-up, any additional surgeries will also be documented. A description of type and location of surgery will be noted. If the surgery involves the injured “study” limb, this will also be recorded.

Analysis	Tube / ml	Day of Surgery	Post-Op Day 6	3 Month Follow-up
Plasma	BD™ P100 / 8.5	X	X	X
RNA	2 x PAXGene RNA / 2.5 ea	X	X	X
DNA	PAXGene DNA / 8.5	X	X	X
Liver Function	BD™ Vacutainer SST / 5.0		X	X
CBC	BD™ Vacutainer K2 EDTA / 3.0		X	X
VPA level	BD™ Vacutainer Serum / 4.0		X	

The -80°C and -20°C freezers to be used are located in Duke South. The -80 °C freezer to be used at Duke is located in Building GSRB1, Room 1003. All research samples will remain in a -80°C freezer at Duke South until they are batch transferred to the lab freezer in GSRB1 at Duke (Van de Ven Lab). Further processing and transfer to Duke core facilities for epigenomic and gene expression assays and to Metabolon for metabolic analysis will occur from our lab in GSRB1.

Research blood samples will be sent to the Duke Center for Human Genetics (CHG) at Duke University in a fully de-identified fashion and are unavailable for clinical purposes. Research blood samples are tracked and stored within our existing Laboratory Inventory Management System (LIMS). The LIMS is designed to track each specimen's precise location, along with details of the type of specimen the tube contains, where the specimen came from, the physical amount of the sample, and any local accession data. All specimens are identified by barcode and are not identifiable except via a coding table (housed in a research folder on the Anesthesiology ‘Parnassus’ shared drive restricted to study team members) held in a different location from either the database or the samples.

Subjects may receive a summary of the study results at the end of the study upon written request to the PI. No individualized information will be analyzed or released to study investigators or participants.

Metabolomic Experiments

In our group we use plasma metabolomic profiling both to prioritize the biochemical pathways important

in the transition from acute to chronic pain, and also to provide continuity between our animal and human work, since mammalian metabolism shares conserved biochemical pathways. We believe this approach may also be used to guide understanding of the response to VPA therapy. These assays will be conducted on de-identified plasma samples by Metabolon Inc. Raleigh, NC. Highly annotated data is returned promptly together with various unbiased class-identification analyses that permit hierarchical organization and interpretation of the biochemical pathways most active and, therefore, most likely involved in the disease subtype (in this case persistent pain presence, subtype and severity).

Epigenomic (DNA methylation) Experiments

DNA isolated from PBMCs will be sodium bisulfite-treated for cytosine (C) to thymine (T) conversion prior to analysis on the Illumina HumanMethylation 450k BeadChip. This chip quantitatively assays methylation at over 485,764 sites spanning the entire genome. Anywhere from 2-8 different CpG dinucleotides are interrogated for each different part of the gene (gene body, untranslated regions, transcription start sites), as well as an average of five sites interrogated/CpG island (CGI) and 2-3 probes interrogated for CpG island "shores". Methylation data are imported into R and normalized using the Methylumi package. Probes with significant differences in methylation level between treatment groups are identified using the Mann-Whitney U test. From this analysis we will be able to determine how closely DNA methylation correlates with our clinical phenotype (namely presence, severity and type of persistent pain syndrome).

Gene Expression Experiments

In order to confirm functional relevance of the differential methylation data, we will measure genome-wide expression of the circulating PBMC transcriptome. These data will permit biological interpretation of the relationships between the epigenetic data and the clinical outcome data. These epigenetic and genomic biomarkers may be considered risk markers of both chronic post injury pain and also response (or failure to respond) to VPA therapy. These findings may inform future therapeutic discovery studies of novel analgesics. We will measure gene expression using the Illumina HumanHT-12 v4 chip, at the Duke CHG and using their iScan platform. Data analysis will be conducted using the Illumina GeneStudio software which provides specifically for convergence analysis between the 450K Methylation array, and the HumanHT-12 expression array.

In summary, we will first prioritize biochemical pathways of interest using unbiased plasma metabolomics to characterize the different patient groups (severe pain, no pain, etc.) according to their plasma metabolomic profile. This approach identifies those pathways that best characterize the biochemical profiles using unbiased plasma metabolites as endophenotypes. These data inform our methylation analyses by prioritizing pathways (and therefore genes, particularly those at known control points) for further scrutiny. We will relate the methylation signatures in these patients' genes, including known inflammatory genes, to circulating metabolites in the plasma samples, in order to determine the functional significance of differential CpG methylation. We will then confirm functional relevance of these epigenetic marks by measuring expression of their respective genes in circulating PBMCs and relating these data to the metabolomic, epigenetic and clinical datasets.

INTERVENTION / TREATMENT

This study will be a prospective, randomized trial of valproic acid for amputation, stump revision, and surgery for limb injury with neurologic damage. "Control" patients will receive standard regional anesthesia catheters (either peripheral nerve or epidural catheter), anesthetic management and a placebo. "Intervention arm" patients will receive standard regional anesthesia catheters (either peripheral nerve or epidural catheter), anesthetic management, and valproic acid 250mg preoperatively, and then three times per day for 6 days post-operatively or until the time of discharge from the hospital. Given the pragmatic nature of this trial, there will be no washout period prior to starting the medication and patients will continue to take their standard perioperative medications. Patients on multiple medications with

significant comorbid disease will not be excluded from the study. There will be no restrictions on activity, hydration or fasting except that dictated by clinical care for that individual. Patients will be without food prior to surgery, and will have diet progressed as tolerated based on surgical recovery.

Treatment Allocation, Study Drug Handling and Randomization

Randomization will be stratified by site and by surgical etiology. At the Duke University Medical Center, patients will be associated to the study in Maestro Care and a study order for the investigational agent will be created; this order will be released and a member of the study team will obtain the study drug/placebo prior to or on the day of surgery. Patients will be randomized when study orders are entered into Maestro Care, and on a sequential basis. Patients will be randomized to either receive oral placebo 3 times per day for 7 days (day of surgery and 6 days following surgery, or until the time of discharge from the hospital), or oral valproic acid 250mg 3 times per day for 7 days (day of surgery and 6 days following surgery, or until the time of discharge from the hospital). At DUMC/DVAMC, 105 patients will be randomized to placebo, and 105 patients will be randomized to receive three times per day doses of valproic acid 250mg for 7 days. The pharmacist will assign treatment class according to the randomization schedule provided by our Statistician. The pharmacist will then dispense study medication in syrup form labeled “study drug” with no indication of the liquid contents and labeled with the patient ID# and, as requested by the Pharmacist, it will be ordered one day before the scheduled surgery if possible. The labeled “study drug” will be kept in a locked Duke Anesthesiology Research Office and then taken to the pre-op area for the first dose to be given.

Drug administration will be performed prior to induction of anesthesia on the day of surgery. Subsequent doses will be administered at the bedside by the ICU or floor nurse depending on patient location. A record will be made in the medication administration record (MAR)/Maestro care. The IDS will retain records of study drug inventory, dispensing records, and intervention allocation.. Additionally, notification in Maestro Care will be entered into the patient’s EMR. All doses of the study drug will be administered by DUMC medical or nursing staff and will be documented. . Patients will complete study drug administration unless they withdraw their consent or either their treating physician or the principal investigator believes it would be dangerous to continue valproic acid. If the subject withdraws during the administration of VPA, they will continue with their current medical regimen without alteration. The Investigational Drug Pharmacist will be the only person aware of treatment allocation until the study data and treatment allocation are unblinded once endpoint adjudication has been completed for all study subjects.

Blood Sample Collection

Clinical blood samples will be used to monitor for safety, and research blood samples will be analyzed for epigenetic and gene expression changes that occur during the postoperative period. Precise biochemical research analyses are described in the section “Analytic Tests”. The initial blood sample will be drawn immediately prior to induction of anesthesia to maximize patient comfort and minimize deviations in the routine care of the patient.

The second blood sample will be obtained at the completion, or early termination, of study drug administration. This sample collection will be performed in the hospital while the patient is still admitted in the routine postoperative care of their surgery or medical disease. The blood draw will be performed either by research study personnel under standard sterile precautions.

A third and final blood sample will be taken at the time of pain clinic follow-up, approximately 3 months after surgery.

Training for Study Personnel

All DUMC training certifications required for study personnel on this study are kept in the study regulatory binder. Also included in our documentation are training certifications for blood collection and handling of biological samples. Prior to start of enrollment, Dr. Buchheit will conduct a meeting for all study personnel involved to review the Standard Operating Procedure (SOP) and answer any questions.

CONFIDENTIALITY AND PRIVACY

Private health information of study participants will be respected and all data analysis will be done in blinded fashion, such that individuals will not be identifiable from the final analysis dataset. As such, the dataset and biorepository will be fully de-identified once the dataset is complete and locked.

Subject Confidentiality Protection

Enrolled subjects will be assigned a barcoded study ID number, unrelated to any Identifiable Protected Health Information (PHI). All data will be entered via Research Electronic Data Capture (REDCap) – a secure, web-based application designed exclusively to support data capture for research studies.

Only de-identified data will be entered using REDCap

Investigators will have secure password protected access to REDCap in order to enter and analyze data.

This study ID number will be used on all the CRF's and to enter data in REDCap. There will be a master list linking the subject with the study ID which will be kept in the secure password protected Parnassus drive. The CRF will be stored electronically using REDCap; only Dr. Buchheit and his research team will have access to this information. A paper copy of the CRF will be stored in a locked file cabinet, at the Duke Anesthesiology Research Office. Only Dr. Buchheit and his research staff will have access to these folders. Additionally, access to patient records and PHI will be terminated for members of the research team who are no longer part of the research team. All research blood samples will be de-identified without any PHI prior to sending to Duke labs, Quest and Metabolon for analyses. The samples will be identified only through a study ID number. Collaborators will not have access to the master list of any identifiers.

PHI for subjects (name, address, SSN only) will be provided to Duke for the issuance of a \$50.00 check for participation in the study after the subject's three-month follow up visit.

In summary, patient records and PHI will be collected at the Durham VAMC, Duke University Medical Center and WRNMMC for patients enrolled at each site. These data will remain within the confines of the respective facility where the patient is enrolled, in a locked filing cabinet with the exception of PHI required to process compensation. Patient data entered in REDCap will be fully de-identified and these data records, along with blood samples identified by a barcode number only, will be analyzed at Duke. Findings and results from de-identified analyses will be shared in the context of standard reporting. All patient data collected in REDCap will be fully de-identified. WRNMMC research staff will not have access to DUMC/DVAMC patient data, nor will research staff at DUMC/DVAMC have access to WRNMMC patient data. Information is collected on Duke's IRB Personal Data Disclosure Form to process payment to subjects. An experimental Subject Payment Form accompanies the IRB Personal Data Disclosure Form and will be signed by the Financial Practices Manager at Duke. These are hand-delivered to Employee Travel & Reimbursement for processing. A redacted copy (the SSN and addresses are redacted) is kept on the secure Anesthesiology Department Grants Folder which is restricted. No PHI is kept other than the name and date of signature (on the redacted form). PHI (except for name), are hidden on the IRB Data Disclosure Form and Experiment Subject Payment Form. The name and date are kept to track the payments and reconcile study charges.

HIPAA Authorization

Protected Health Information (PHI) and the following HIPAA identifiers will be collected:

 X 1. Names

☒ 2. Street address, city, county, 5-digit zip code

☒ 3. Months and dates (years are OK) and ages >89 (unless all persons over 89 years are aggregated into a single category)

☒ 4. Telephone numbers

☐ 5. Fax numbers

☐ 6. E-mail addresses

☒ 7. Social security number

☐ 8. Medical record number

☐ 9. Health plan beneficiary number

☐ 10. Account number

☐ 11. Certificate/license number

☐ 12. Vehicle identification number (VIN) and/or license plate number

☐ 13. Device identifiers and serial numbers

☐ 14. URLs (Uniform Resource Locators)

☐ 15. Internet protocol address number

☐ 16. Biometric identifiers, such as finger and voice prints

☐ 17. Full face photographic images or any comparable images

☐ 18. Any other unique identifying number, characteristic, or code such as patient initials

Research subjects will need to sign a HIPAA Authorization.

DATA HANDLING AND ANALYSIS

Statistical Consideration

This is a randomized double blind phase II trial in which 420 patients will be randomized with equal probability to treatment arm or controlled placebo arm. The primary objective is to compare the incidence of chronic neuropathic and post-amputation pain at 3 months after surgery between valproic acid (treatment) and placebo (control) arms.

Sample Size Justification

The primary hypothesis is that we anticipate the patients treated with valproic acid will have a significantly lower incidence of chronic pain 3 months after surgery compared to the patients with placebo (in control arm). We will use the average pain score over the past week as noted on the Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) as the primary outcome measure. We will define the primary endpoint as the incidence of chronic pain at the 3-month evaluation point. Chronic pain will be defined as an S-LANSS average pain score of 3 points or greater. We anticipate that approximately 60% of the non-treatment arm patients will develop chronic pain based on the incidence of post-amputation pain noted in the literature and our observational research data. We also anticipate a 10% drop-out rate at 3 months secondary to death and loss to follow up. Thus 378

evaluable patients (189 patients in each arm) at 3 month after surgery will be available for analysis in this study. With a type 1 error rate of 0.05 and the above assumptions, this study will have 83% power to detect the minimal difference in incidence of 3-month chronic pain of 15% (45% vs 60%) between two arms using a two-sided chi-square test.

Data Analysis Plan

The primary endpoint is the incidence of chronic pain at the 3-month evaluation point, and the chronic pain will be defined as an S-LANSS average pain score of 3 points or greater. Secondary endpoints will include the numeric scores from forms BPI, S-LANSS, DVPRS and RASS and the change in these scores from baseline to 3 months, as well as the incidence of neuropathic limb or post-amputation pain at 1 and 6 months after surgery. Frequency and percentage of the categorical variables in above endpoints will be reported by treatment arm and by assessed time. Mean, standard deviation and range of the mean scales of the above forms, as well as the changes of mean scales from baseline will be computed by arm and by assessed time. Two-sample chi-square tests will be used to assess the treatment difference of the primary endpoint and post-amputation pain (or neuropathic pain) at each time. Logistic regression will be applied to investigate the treatment difference on the primary endpoint and post-amputation pain by adjusting for potential prognostic variables including baseline pain level, study site, type of surgery, diabetes, and intervening therapies. Similar analyses will be carried out in study subgroups of site, surgery type, and diabetic status. Two sample t-tests will be used to assess treatment difference in changes of mean scales from baseline. In addition, linear regression will be used to assess the treatment difference on changes of mean scales from baseline by adjusting for covariants. P values of less than 0.05 will be considered to indicate statistical significance. Intent-to-treat analysis will be performed. Sensitivity analyses will also be carried out by excluding patients who drop out before 3 month post-surgery. If the dropout rate is larger than 10% and if there is evidence that the missing mechanism is not MCAR (missing completely at random) but MAR (missing at random), multiple imputation will be conducted. We will have the statistical support from William White MPH, Statistician at Duke University for the clinical trial phase of the study, and the laboratory of Simon Gregory PhD at the Duke Center for Human Genetics for the genomic and epigenomic analysis.

Interim Analysis Plan

Interim analysis will be conducted when 50% of the data are collected. The incidence of chronic pain at 3 months will be estimated after 189 patients have submitted information for the primary endpoint. The interim analysis is to test if VPA worsens post amputation pain as compared to the placebo. Repeat confidence interval approach will be used. At the interim analysis, 97.5% one-sided confidence intervals around the difference of the post amputation pain rates at 3 months between the placebo and experimental arm will be computed, using the O'Brien-Fleming critical value to determine the confidence width. If the confidence interval does not cover the target alternative of 0.15, the trial will be stopped early.

Accrual

We anticipate enrolling 50% of the study subjects (210 subjects) at the DUMC/DVAMC with a recruitment rate of 5-6 subjects per month, over a 36-month duration.

Epigenetic Analysis

CpG DNA methylation (DNAm) data are interpreted using GenomeStudio to quantify methylated (M) and unmethylated (U) signal intensities for genomic DNA. Overall methylation levels (β) are calculated as the ratio of methylated to total signal (i.e. $\beta = M / (M + U)$) where β ranges from 0 (unmethylated) to 1 (methylated). Quality control of data generally results in removal of samples with aberrantly low signal intensity (mean less than 2,000) and/or fewer CpG loci with detected signal relative to background. Assay controls are inspected to remove samples with poor bisulfite conversion, staining, extension (single nucleotide extension assay), hybridization, or specificity. Furthermore, outliers identified by

hierarchical clustering and/or dissimilarity matrices are removed. In a previous study in the CHG, from a total of the 458 samples, 420 passed QC. Additionally, we generally run one control DNA replicate on each bead chip to assess overall assay reproducibility. Methylation profiles of the control DNA has correlated well in our previous experiments, generating an average Pearson correlation coefficient (R) of 0.992 both within and between experiments. We will control for false positives using the false discovery rate technique described in detail by Devlin et al.¹⁸ This allows control of overall significance by calculating the positive association rate expected by chance, and controlling the test P value for this rate.

Data Collection

The data to be collected are described below. All investigators and co-investigators are trained to collect all the data and administer the pain questionnaires.

The following information will be collected by reviewing the chart in combination with the initial subject interview:

- **Demographics** (name, address, telephone number, SSN, gender, ethnicity/race, age, Body Mass Index)
- **Significant medical and surgical history.** The Charlson comorbidity form will be used.¹⁹ This is a well validated and widely used method of assigning weights to comorbid disease such that one or more pre-existing conditions do not dominate the outcome measurement.
- **Current narcotic medication.** (Total daily morphine equivalent dose) This is a more objective way of measuring the impact of a pain state on an individual than verbally reported pain score. Opioids must be prescribed which means there is at least some professional assent of the pain's severity. This will be used as an endpoint variable.
- **Current non-narcotic medications.** We will record use of anticonvulsants, tricyclic antidepressants, beta-blockers, non-steroidal anti-inflammatory medications, corticosteroids or fish oil supplements. These medications may have an impact on pain severity and will be used in the secondary outcome analyses.

Pain Questionnaires to be completed by the subjects:

- **Brief Pain Inventory (BPI) short form²⁰**

The BPI short form is a multidimensional patient-completed measure that assesses the sensory component of pain intensity (average over the last week, worst and least, and present pain) using a numeric rating scale (0=No pain to 10=Pain as bad as you can imagine), percentage of pain relief (0=No relief to 100%=Complete relief) and pain interference or reactive component with aspects of daily living. For the evaluation of pain interference, 7 'interference items' concerning work, activity, mood, enjoyment, sleep, walk and relationships are assessed using 0-10 numeric scales (0=No interference to 10=Complete interference). Acceptable reliability and construct and criterion validity exists for populations with chronic non-malignant pain.

- **Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS)²¹**

The S-LANSS is a self-reported version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale. It aims to differentiate neuropathic pain from somatic or nociceptive pain. The S-LANSS correctly identifies 80% of patients with neuropathic pain when used in interview format. It is established as a valid measure of symptoms and signs in neuropathic pain that allows comparisons with other investigational measures. This comparison leads to insight between the relationship between pathophysiologic mechanisms and clinical manifestations of pain. It has been validated in outpatients with neuropathic pain.²¹ The usefulness of the S-LANSS is in differentiating neuropathic pain from nociceptive pain, which makes this instrument ideal for the proposed study.

- **Patient Health Questionnaire-2 (PHQ-2)²²**

The PHQ-2 is a validated instrument that inquires about the frequency of depressed mood. Although brief, it has been found to be a valid screening tool for depression, and requires significantly less time for completion than other depression assessment tools.

- **Complex Regional Pain Syndrome²³ and Neuroma Questions**

We will use the “Budapest Clinical Criteria” for this study, which have been recently validated with a sensitivity of 0.99 and specificity of 0.68 in the detection of Complex Regional Pain Syndrome.

- **Phantom and Residual Limb Pain Questions²⁴**

The phantom and residual limb questions have been studied and validated in a population study of 437 lower extremity amputees as part of the Groningen Questionnaire Problems Leg Amputation (GQPLA) study. It is widely used in detection and assessment of amputation-related pain.

- **Defense and Veterans Pain Rating Scale (DVPRS)²⁵**

The DVPRS is a pain assessment tool developed by the military in an effort to improve reliability and interpretability of pain assessment in the military population. It has been found to be an effective and valid tool in this population.

- **Richmond Agitation-Sedation Scale (RASS)²⁶**

The RASS is a commonly used, valid and reliable assessment tool for use in hospitalized patients. Validity testing reveals good inter-rater reliability among medical, surgical, and intensive care units.

Physical Exam: to be completed at study enrollment, 3 and 6 month visits

The investigators will perform an exam of the affected limb by removing the prosthesis and/or dressings. This will not apply to dressings for open wounds/infected areas.

- **Visual inspection:** will be performed of the affected limb, noting asymmetry of sweating, color, skin changes, hair growth, and tremor.
- **Allodynia:** Clean cotton wool will be gently brushed against the skin in the painful area (if present) of the affected limb. If a painful area does not exist, testing will be performed in an area above the distal injury. The skin will be brushed in a straight line of approximately 2 cm and this process will be repeated 3 times. Allodynia will be noted if any of the 3 brushes are painful or unpleasant to touch. The cotton wool will be discarded after use.
- **Tinel’s Sign:** The investigator will then gently tap on the painful area of skin (if present). If a focal area of “pins and needles” or nerve sensitivity is noted, it will be considered to be Tinel’s POSITIVE.
- **Sensory and Motor Deficit:** For exam of an injured, non-amputated limb, evidence of sensory deficit outside of the area tissue injury or motor deficit will be noted.

PHENOTYPE ADJUDICATION

Adjudication of Clinical Endpoint

Adjudicating Panel: Voting members: Thomas Buchheit, Chester “Trip” Buckenmaier, Thomas Van de Ven, David Macleod, Hung-Lun (John) Hsia, and Matthew Mauck. A quorum for adjudication will include any 3 of the above 6 members.

Phenotype Adjudication Process: Study subjects will be assessed at time of enrollment and at 3 months for endpoint determination of the presence or absence of chronic phantom, residual limb, or injured limb pain. If the subject has an unhealed surgical wound or surgical wound complication, the adjudication process will be moved from 3 to 6 months to allow for wound healing. If the subject continues to have unhealed wounds at 6 months, the adjudication will take place, noting the presence of

non-healing wound or infection. The adjudication panel will be convened for the express purpose of endpoint determination, and subjects will be assessed in a step-wise fashion using the Duke Post-Amputation Pain Algorithm. Each patient enrolled in the study will be discussed and their respective status (met primary endpoint or did not meet primary endpoint) will be adjudicated utilizing the data collected during the standardized assessments and according to the following rules. A majority vote will determine the formal endpoint. (See Appendix for Adjudication Flow Chart)

Process for Phenotype Adjudication

- Step 1 Identify patient as Amputation vs Injured Limb
- Step 2 Identify patients with pain vs no pain
- Step 3a Identify Amputation patients as either/both phantom limb pain (PLP), residual limb pain (RLP)
- Step 4a For Amputation patients, exclude RLP subjects with only somatic pain by using the Self-Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS)
- Step 5a For Amputation patients, categorize neuropathic residual limb pain type: 1) Neuroma, 2) Complex Regional Pain Syndrome or 3) Mosaic Neuralgia (neuralgia not otherwise specified)
- Step 3b For Injured-Limb Pain patients, exclude patients with only somatic pain by using the Self-Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS)
- Step 4b For Injured-Limb Neuropathic Pain, categorize pain type as: 1) Neuroma, 2) Complex Regional Pain Syndrome, or 3) Mosaic Neuralgia (neuralgia not otherwise specified)

Pain State Definitions:

- a. Neuroma pain will be defined as pain localized to the site of a nerve transection or nerve injury (positive Tinel's sign).
- b. Complex Regional Pain Syndrome (Budapest clinical criteria), will be defined as persistent pain with symptoms in 3 of the 4 following categories: Sensory, Vascular, Sweating/Edema and Motor/Trophic. Additionally there should be physical exam signs in 2 of the 4 following categories: Sensory, Vascular, Sweating/Edema, or Motor/Trophic.
- c. Mosaic Neuralgia pain will be defined as neuralgic pain, not associated with an identifiable neuroma or focal neuralgia, and not meeting criteria for CRPS.

INFORMATION MANAGEMENT AND ANALYSIS SOFTWARE

All data will be de-identified and entered via Research Electronic Data Capture (REDCap) which is a secure, web-based application designed exclusively to support data capture for research studies. Data are housed on Duke Health Technology Solutions (DHTS) servers providing secured data. The Duke Translational Medical Institute (DTMI) installation of REDCap has been validated and meets DTMI's understanding of HIPAA-compliance. We are successfully using this data collection system in our current DMRDP project in amputation pain.

Investigators will have secure password protected access to REDCap in order to enter and analyze data. The data collected in REDCap will be held as an electronic case report form (eCRF) and hard copies will be printed and maintained in a patient shadow chart kept in a locked file cabinet in the Duke Anesthesiology Research Office.. In this way a permanent record will be kept of the patient's involvement

in the trial, and their trial data will be verifiable for future audit purposes. Analysis of clinical study data will be carried out using SAS® v9.2 statistical software with a de-identified download from REDCap. Data stored in REDCap at Duke will be used to link to the epigenetic data developed by the Center for Human Genetics (CHG). All of these data shared with CHG will be fully stripped of all 18 HIPAA identifiers. Private health information of study participants will be respected and all data analysis will be done in blinded fashion, such that individuals will not be identifiable from the final analysis dataset. Each patient will be allocated a study ID number when they sign a consent form, and thereafter will be referred to by that number. Investigators will have secure password protected access to REDCap in order to enter data. The dataset and biorepository will be fully de-identified once the dataset is complete and locked.

Research blood samples are tracked and stored within our existing Laboratory Inventory Management System (FreezerPro). The LIMS is designed to track each specimen's precise location, along with details of the type of specimen the tube contains, where the specimen came from, the physical amount of the sample, and any local accession data. All specimens are identified by barcode and are not identifiable except via a coding table held in the password-protected folder on the secure Duke shared Drive, Parnassus, and available only to Dr Buchheit's research team. Specimens will be destroyed at the end of study in accordance with the Duke requirements.

Data Quality Control

It is our policy that all inclusion and exclusion criteria are verified by a second clinically trained individual within our group. This practice has effectively eliminated the enrollment of ineligible patients into clinical trials within our group.

We also routinely audit a selection of clinical trial subjects in order to track accuracy of data collection, percentage of missing data fields, compliance with institutional (and where appropriate sponsor) requirements and adverse event reporting. Use of the REDCap system (see appendix material) enhances our ability to track this information as it provides an automatic audit trail as well as automatic reporting of % fields complete.

HANDLING OF UNEXPECTED OR ADVERSE EVENTS

IDENTIFYING AND REPORTING ADVERSE EVENTS

Data and Safety Monitoring Board (DSMB)

A DSMB will be established and will be comprised of Dr. Rebecca Schroeder, Dr. Jonathan Mark (Chief of Anesthesiology at the DVAMC) and Dr. David Lindsay (Duke Pain Medicine Fellowship Director). Dr. Schroeder is ideally suited to lead this monitoring board given her position as the Clinical Director of the Duke Perioperative Informatics Initiative.. None of the board members are part of the investigative team.

The DSMB will meet annually after the start of enrollment, to review the progress and timeliness of the trial, and to insure that adverse events, side effects and mortality are closely monitored. One of these annual meetings will be scheduled within 3 months after 50% of subjects have been enrolled, and will include the specific review of the primary endpoint in addition to the yearly data and safety review.

In addition, Dr. Schroeder will also serve as the DoD Research Monitor for this study. She will be responsible for the following actions:

- Observe recruitment and enrollment procedures and the consent process for individuals, groups or units, overseeing study interventions and interactions,
- Review monitoring plans and any reporting of unanticipated problems involving risk to human research subjects or others.

- Oversee data matching, data collection, and analysis
- Discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research;
- Have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report;
- Have the responsibility to promptly report observations and findings to the IRB or other designated official and the HRPO.

Toxicity Monitoring

Unacceptable drug related toxicity rates will be compared between two arms. It is assumed that the incidence of unacceptable toxicity in patients treated with valproate is 10%. If at any scheduled time of analysis the lower boundary of the one-sided 90% confidence interval for the difference in unacceptable toxicity rates between the treatment and controlled arm exceeds 10%, accrual to the trial will be immediately suspended, the toxicity data will be reviewed, and a decision by the DSMB will be made about whether it is safe to resume accrual.

Response to Unexpected Findings

Risks of this study have been minimized by combining the current standard-of-care treatment for limb surgery with an FDA approved medication used at military and veteran medical centers. This is a study of a new indication for this well-established medication. That being said, any medication administration can have side effects. VPA has known side effects of sedation, confusion, and the remote possibility of organ toxicity. One of the major toxicities known is that of potential teratogenicity if given to pregnant women.

Acute sedation or confusion may occur with study drug administration during postoperative hospitalization. The risk of sedation will be minimized by starting all medications while the patient is admitted to the hospital. Patients will also be monitored for several days during the perioperative period, and will have ample opportunity to discontinue the study medication if they experience significant side effects. In this manner, the risks of sedation or confusion in an unmonitored setting (home) will be minimal. If altered mental status or confusion is noted, the medication will be discontinued and the patient will be withdrawn from the study. Follow-up and continuing care will be coordinated with the admitting surgeon in consultation with the patient's primary care physician.

Increased risk of birth defects including neural tube defects has also been noted in pregnant women on valproate. This risk will be minimal as elective and semi-elective amputations are not performed during pregnancy. Additionally, a pregnancy test will be performed on all women of childbearing potential if not already done in the pre-operative period within 48 hours of surgery. If this is positive, the elective surgery is cancelled. If the surgery is performed under emergency circumstances, the patient will be excluded from the study.

Although rare, late organ toxicity has also been noted with patients on chronic VPA. We will minimize these risks by administering the study drug for only 7 days. A patient will be excluded from the study if he/she is noted to have significant liver dysfunction preoperatively (see exclusion criteria). Monitoring for organ toxicity will be performed according to the chart on page 14 with laboratory analysis for blood count, liver function tests and tricyclic antidepressants if indicated secondary to high dose. If organ toxicity is noted during the study period, this will be recorded as an adverse event by Dr. Buchheit. The primary care physician will be notified for longitudinal follow-up of the laboratory abnormality, and a Hepatology consult will be requested if indicated.

Peripheral phlebotomy carries little risk of serious or unexpected adverse events. Bleeding, swelling and localized pain are the most common adverse events. Some subjects may feel dizzy and lightheaded but these are typically mild and self-limited.

Asking subjects about pain and other psychological issues may cause psychological distress. If the investigator notices increased anxiety and stress, the investigator may contact the subject's primary care provider for further evaluation. In particular, if evidence of suicidal ideation and or severe depression is elicited, an urgent referral to their primary care provider will be made.

Expected adverse events, which are not serious, will be reported yearly on the Annual Progress Report (APR) for each protocol. A summary of all serious or unexpected side effects will also be included in the APR. If there were no adverse events, this will be stated on the APR.

Identifying, Managing and Reporting Problems

All findings of serious non-compliance will be reported to the Director, Defense Research and Engineering as well as the DUMC IRB.

Any protocol deviations during the course of the study will be reported to the DUMC IRB per their guidelines.. All information security and privacy incidents will be reported immediately Duke IRB and Duke Office of Clinical Research (DOCR)..

Emergency Care

Since all patients will be treated at the Duke University Medical Center, they will have access to full spectrum care. If an adverse event or study related injury occurs, they will follow up with the study team and their primary care physician for standard management. If required, this would include access to emergency services, critical care services and all other necessary hospital and outpatient functions,. Additionally, gastroenterology and hepatology consults will be obtained when needed through Dr Steve Choi.

Given the short nature of the treatment period, pharmacologic pregnancy prevention will not be needed. Nonetheless, if patients are female of child-bearing age, they will be counseled to use birth control in the unlikely situation of sexual activity during the 7 day postoperative period following amputation or limb surgery.

If the subject complains of significant pain that is not being addressed by a health care provider and or having severe depression an urgent referral to their primary care provider will be made. If the subject describes having suicidal ideation, an urgent referral to the primary care physician and/or psychiatry service through the Emergency Department will be made.

DISSEMINATION, NOTIFICATION AND REPORTING RESULTS

If the clinical trial does not demonstrate a significant advantage for the use of VPA in this patient population, we will continue to analyze the biomarker and epigenetic data, searching for markers of risk for the development of chronic pain after nerve injury. We believe that a greater mechanistic understanding of these epigenetic processes will ultimately lead to future targeted therapies in a personalized medicine approach to the treatment of nerve injury pain.

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APPENDIX MATERIALS

DATA COLLECTION FORMS

Brief Pain Inventory (BPI)
Self-Reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS)
Patient Health Questionnaire-2 (PHQ-2)
Defense and Veterans Pain Rating Scale (DVPRS)
Complex Regional Pain Syndrome Questions
Neuroma Questions
Phantom Limb Pain Questions
Residual Limb Pain Questions
Richmond Agitation Sedation Scale (RASS)
Charlson Comorbidity Score
Body Diagram
Adjudication Chart
Telephone scripts
Abbreviated Mini Mental State Examination (MMSE)
Demographics
Exam and Visual Documentation at Enrollment
Active medications (Narcotic and Non-narcotic)
Medical History
Amputation injury at enrollment
Phantom Limb Pain
Prosthesis
Residual Limb Questions



IRB NOTIFICATION OF AMENDMENT APPROVAL

Amendment ID: Amd008_Pro00047194
Principal Investigator: Thomas Buchheit
Protocol Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
Sponsor/Funding Source(s): US Department of Defense
Federal Funding Agency ID: W81XWH-12-2-0129
Date of Declared Concordance with federally funded grant, if applicable: N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

Activity:	Amendment	Review Type:	Expedited
Review Date:	8/21/2014		
Issue Date:	8/21/2014		
Expiration Date:	8/28/2014		

DUHS IRB approval encompasses the following specific components of the study:

Protocol, version/date:	--
Summary, version/date:	--N/A
Consent form reference date:	--N/A
Investigator Brochure, version/date:	--
Pediatric Risk Category:	--
Other:	--Revised Section 10 - Enrollment Increase

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

No change to the protocol, consent form or other approved document may be implemented without first obtaining IRB approval for the change. Any proposed change must be submitted as an amendment. If necessary in a life-threatening situation, where time does not permit your prior consultation with the IRB, you may act contrary to the protocol if the action is in the best interest of the subject. You must notify the IRB of your action within five (5) working days of the event.

The Duke University Health System Institutional Review Board for Clinical Investigations (DUHS IRB), is duly constituted, fulfilling all requirements for diversity, and has written procedures for initial and continuing review of human research protocols. The DUHS IRB complies with all U.S. regulatory requirements related to the protection of human research participants. Specifically, the DUHS IRB complies with 45CFR46, 21CFR50, 21CFR56, 21CFR312, 21CFR812, and 45CFR164.508-514. In addition, the DUHS IRB complies with the Guidelines of the International Conference on Harmonization to the extent required by the U. S. Food and Drug Administration.



DUHS Institutional Review Board
2424 Erwin Rd | Suite 405 | Durham, NC | 919.668.5111
Federalwide Assurance No: FWA 00009025



IRB NOTIFICATION OF AMENDMENT APPROVAL

Amendment ID: Amd007_Pro00047194
Principal Investigator: Thomas Buchheit
Protocol Title: Regional Anesthesia and Valproate Sodium for the Prevention of Chronic Post-Amputation Pain
Sponsor/Funding Source(s): US Department of Defense
Federal Funding Agency ID: W81XWH-12-2-0129
Date of Declared Concordance with federally funded grant, if applicable: N/A

The Duke University Health System Institutional Review Board for Clinical Investigations has conducted the following activity on the study cited above:

Activity:	Amendment	Review Type:	Expedited
Review Date:	7/25/2014		
Issue Date:	7/26/2014		
Expiration Date:	8/28/2014		

DUHS IRB approval encompasses the following specific components of the study:

Protocol, version/date:	--VAv28_Duke3 - 7/24/2014
Summary, version/date:	--N/A
Consent form reference date:	--N/A
Investigator Brochure, version/date:	--
Pediatric Risk Category:	--
Other:	--

The DUHS IRB has determined the specific components above to be in compliance with all applicable Health Insurance Portability and Accountability Act ("HIPAA") regulations.

This study expires at 12 AM on the Expiration Date cited above. At that time, all study activity must cease. If you wish to continue specific study activities directly related to subject safety, you must immediately contact Dr. John Falletta or Jody Power. Continuing review submissions (renewals) must be received by the DUHS IRB office 60 to 45 days prior to the Expiration Date.

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Federalwide Assurance No: FWA 00009025

Regional Anesthesia & Valproate Sodium for the Prevention of Chronic Post-Amputation Pain

Log #PT110575

Award Number W81XWH-12-2-0129



PI: Thomas Buchheit MD

Org: Duke University

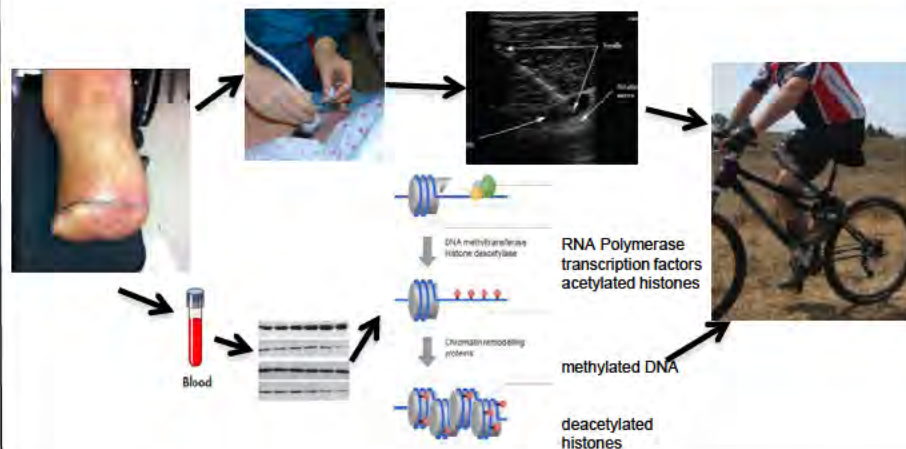
Award Amount: \$2,237,227

Study/Product Aim(s)

- Aim 1: Determine the efficacy of valproic acid combined with regional anesthesia in reducing the incidence of chronic post-amputation pain.
- Aim 2: Determine role of epigenetic DNA methylation in post-amputation pain and effects of valproic acid treatment

Approach

- In a randomized clinical trial, we will determine if the combination of valproic acid combined with regional anesthesia reduces the incidence of chronic post-amputation when compared with regional anesthesia alone.
- We will analyze DNA methylation patterns of patients with post-amputation pain and determine the way they are modified by valproic acid. We will confirm the functional relevance of these modifications using gene expression signatures.



Accomplishments: 1. Submission and IRB approval at Duke, and DoD budget approval for enrollment at Duke University Medical Center; 2. Accelerated enrollment at Duke/VA secondary to Collaborative relationship with Limb-Loss Team that cares for over 400 new amputees/year.

Timeline and Cost

Activities	CY	13	14	15	16
VA/Duke/HRPO approvals; Durham VA/Duke CRADA approved. Enrollment has begun					
*Enrollment/data collection at VA; *HRPO approval/enrollment at WRNMMC					
Enrollment and data collection, initial analysis					
Clinical study closure, outcomes analysis, final adjudication					
Estimated Budget (\$K)		\$391K	\$658K	\$692K	\$497K

Goals/Milestones

CY13 Goal – Protocol planning, data use agreements, IRB & HRPO approvals, lab supply purchasing and enrollment

- ☒ Fully planned, IRB approval at Duke & Durham VAMC, lab supplies purchased and lab analyses developed. CRADA between VA & Duke approved.

CY14 Goals – Patient enrollment, data and sample collection

- ☒ 1st patient enrolled 12/13 at Durham VAMC
- ☒ IRB approval & HRPO secondary approvals complete at WRNMMC
- ☒ Duke approved as enrollment site 02Oct2014, First patient enrolled 15Oct14

CY15 Goal – Patient enrollment, data collection, epigenetic analysis

- ☐ Enrollment, initial epigenetic analysis and endpoint adjudication

CY16 Goal – Clinical study closure and outcomes analysis

- ☐ Final epigenetic analysis and endpoint adjudication
- ☐ Clinical outcomes analysis

Budget Expenditure to Date (from start to date)

Projected Expenditure: \$1,049,000

Actual Expenditure: \$ 694,000

Updated: October 27, 2014